Fever of unknown origin (FUO)

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is a free educational platform, an offering shaped by personal experience, informed by scientific literature and enriched by publicly available knowledge.

We walk in the light cast by giants, visionaries whose tireless pursuit of truth has illuminated the intricate beauty of medicine and microscopy.

This work pays homage to the researchers clinicians and educators whose insights form the bedrock of our understanding. Each image, each reflection echoes their enduring legacy.
All sources are acknowledged with gratitude and intellectual contributions are credited with full respect for legal and ethical standards.

Ibrahim Zardawi MD

Bachelor of Medicine, Bachelor of Surgery (MB ChB) University of Baghdad, Iraq, Master of Science in Pathology (MSc) University of Baghdad, Iraq, Fellow of the Royal College of Pathologists of Great Britain, Fellow of the Royal College of Pathologists of Australasia, Fellow of the International Academy of Cytology, Diploma in Cytopathology, Royal College of Pathologists of Australasia, Founding Fellow of the Faculty of Science of the Royal College of Pathologists of Australasia, Fellow of the College of the American Pathologists FCAP, Fellow of the American Association of Clinical Pathologists, Diploma of the European Board of Pathology

Body Temperature

Normal variation

Body temperature varies between individuals and throughout the day by up to ~2°F or 1.1°C

Average body temperature is ~98.6°F or 37°C

Normal range is 97.5-99.5°F or 36.4-37.5°C

Early morning (4-6 AM) ~97.6°F (36.4°C)

Early evening (4-6 PM) ~99.1°F (37.3°C)

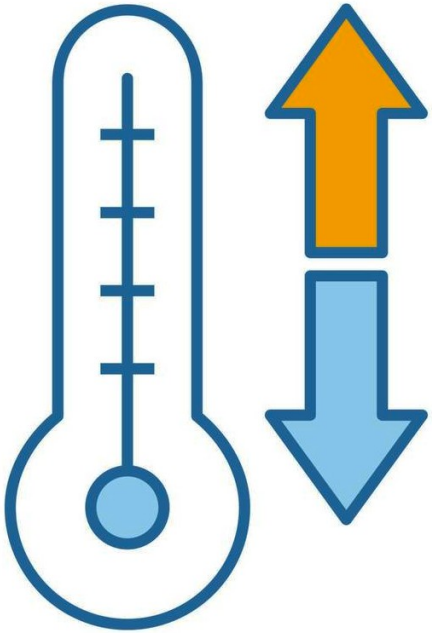
Children typically have higher temperatures than older people

Fever

Temperature of **100.4°F (38°C)**, taken orally is often the **threshold used to define a fever**

Pyrexia?

- **Elevated body temperature** above the normal range
- Caused by resetting of the **hypothalamic thermoregulatory center**
- Represents a controlled physiological **response to infection and other injuries**



Thermoregulation

Hypothalamus functions as the body's thermoregulatory center **(thermostat)**

Thermoreceptors in the hypothalamus detect **temperature changes**

Maintains stable core temperature (98.6°F or 37°C) by

- Heat conservation and generation
  - **Increases heat production** (shivering and increased metabolic rate)
  - **Decreases heat loss** (vasoconstriction and reduced sweating)
- Heat Dissipation (cooling)
  - **Sweating and vasodilatation**

Pathophysiology of Fever

Pyrogens induce fever

Exogenous pyrogens

Derived from infectious agents (micro-organisms, toxins)

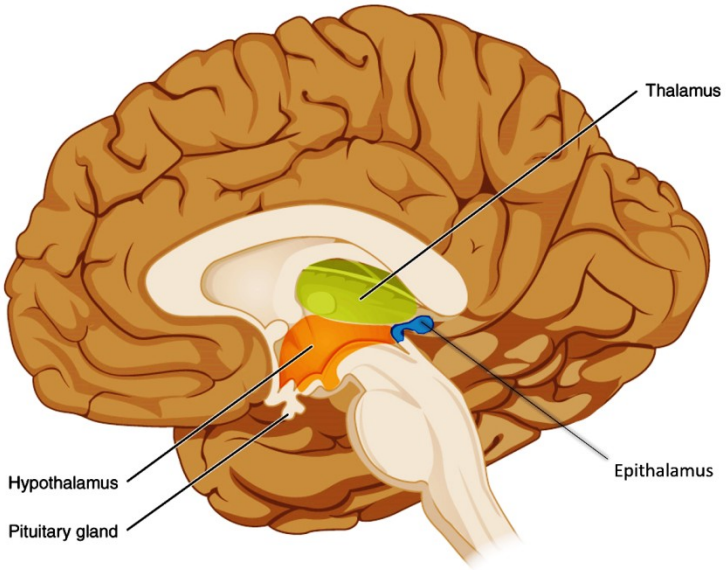
Endogenous pyrogens

Cytokines (**IL-1, IL-6, TNF-α and INF-γ)** released by activated immune cells in response to infectious agents or other insults

Pyrogens stimulate **Prostaglandin synthesis** in the hypothalamus

Prostaglandins raise **thermoregulatory set point**

Result in fever



Pathophysiology of fever

Pyrogens are fever inducing substances

Exogenous (bacterial endotoxins, viruses)

Endogenous (cytokines like IL-1, IL-6, TNF-α)

Pyrogens are detected by **immune cells**

⬇

Immune cells release **cytokines**

⬇

Cytokines stimulate the **hypothalamus** to produce **prostaglandins**

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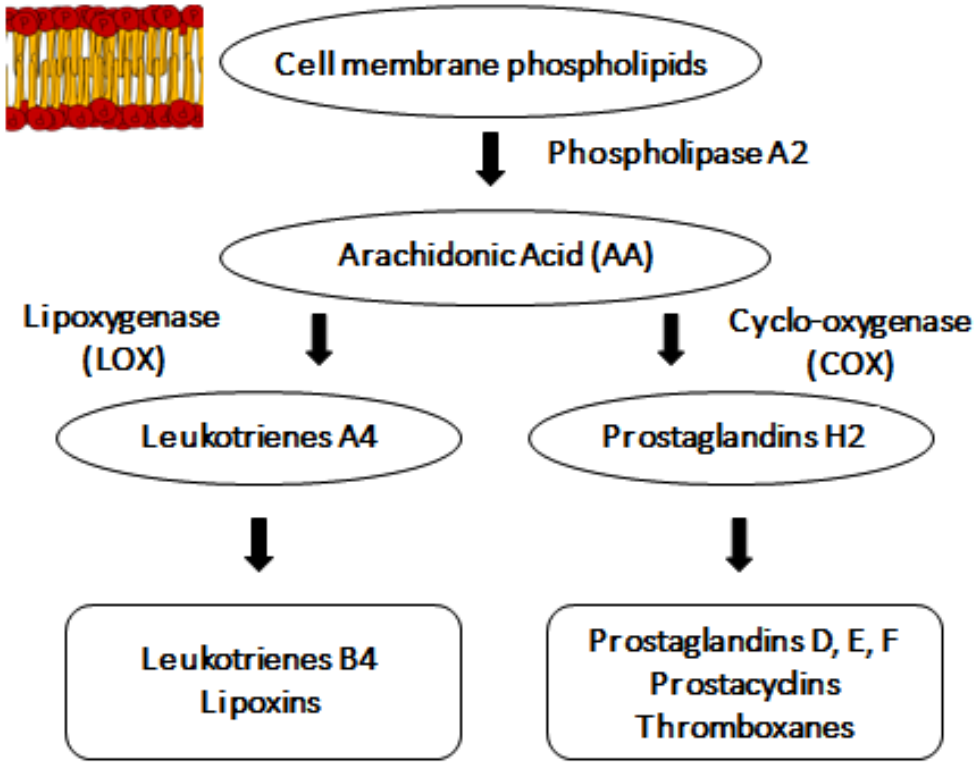
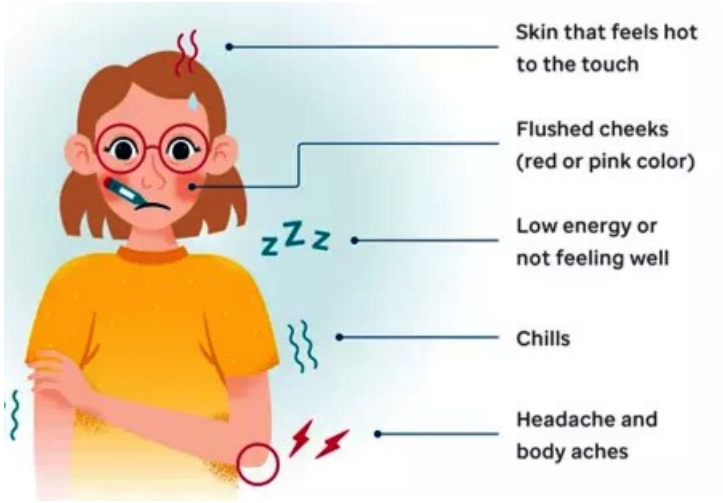
Prostaglandins elevate of the temperature set point by responses such as **vasoconstriction, shivering, etc**

Where do prostaglandins come from?



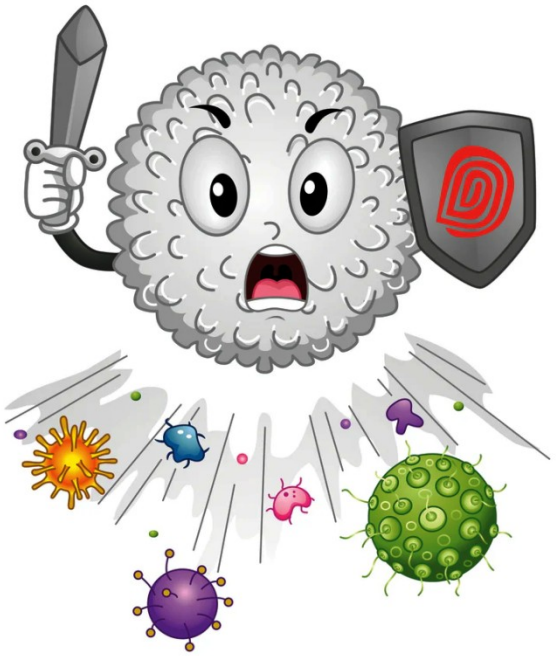
Leukotrienes	Prostaglandins
Eicosanoids produced by **leukocytes**	Eicosanoids produced by **all cell types**
Generated from arachidonic acid by **Lipoxygenase (LOX)**	Generated from arachidonic acid by **cyclo-oxygenase (COX)**
Allergic reaction & sustained inflammatory responses	**Vasodilatation, smooth muscle regulation and inflammation**

Effects of Fever on Metabolism	
Metabolic impact	For every 1°C (1.8°F) temperature rise, metabolic rate increases by ~15% and oxygen consumption also increases by ~15%
Consequences of raised metabolism	Dehydration (water loss) Appetite suppression Deplete energy sources Convert proteins and fats into energy Weight loss
Clinical implications	Need for adequate hydration Increased caloric requirements Nutritional concerns during prolonged fever


Skin that feels hot to the touch
Flushed cheeks (red or pink color)
zZz
Low energy or not feeling well
Chills
Headache and body aches

Symptoms of Fever		
Causes of symptoms	Non-specific Symptoms	Features of the Underlying Illness
Release of inflammatory mediators from macrophages & lymphocytes Temperature elevation	Muscle aches Headaches Shivering Skin tenderness	Irritating rash of chicken pox Cough from a chest infection Pain from a sore throat

Effects of Fever	
Beneficial effects of fever	Increases leukocyte mobility Enhances phagocytosis Decreases endotoxin effects Increases T cell proliferation Enhances interferon activity
Fever as defense mechanism	Enhanced immune cell function Reduced microbial growth Iron sequestration Increased Hepcidin production Reduced iron absorption and recycling Limits nutrient availability for pathogens



Principles of fever treatment
Centrally by giving **an antipyretic (NSAIDs)** which affects the **temperature regulatory centre** in the **hypothalamus** by inhibiting **prostaglandin** production
Peripherally by taking off warm cloths, fanning the individual, giving cool drinks or putting them in a bath of tepid water

Should we treat fever

Arguments FOR Fever Control

- **May reduce metabolic demands** during critical illness
- **Can prevent complications in specific populations** (neurological injuries, elderly)
- **Provides symptomatic relief**

Arguments AGAINST Fever Control

- **Recovery is more rapid** from infections or critical illness
  Fever has been conserved during evolution with **advantages for host defense**
- **Immunological reactions** are sped up by higher temperature
- **Some pathogens with strict temperature preferences** are hindered
- **Aggressive fever control may be detrimental** depending on clinical situation

Fever (pyrexia) of unknown origin
William Osler first coined the term "fever of unknown origin" in **1930** **FUO** was originally used primarily in the **context of hospital settings** **10% of hospitalized patients with fever** fall under this category
Original dentition **Petersdorf & Beeson, 1961**
Temperature of 101°F (38.3°C) or higher on several occasions Fever persisting for >3 weeks Undiagnosed despite after **1 week of inpatient investigation in hospital**

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Modified definition **Durack & Street, 1991**
Temperature of 101°F (38.3°C) or higher on several occasions Fever persisting for >3 weeks Undiagnosed pyrexia **after 3 days of inpatient investigation or 3 outpatient visits**
Classical FUO (original FUO) Nosocomial FUO (hospitalized patients) Neutropenic FUO (<500) HIV-associated FUO (fever of >4 weeks)

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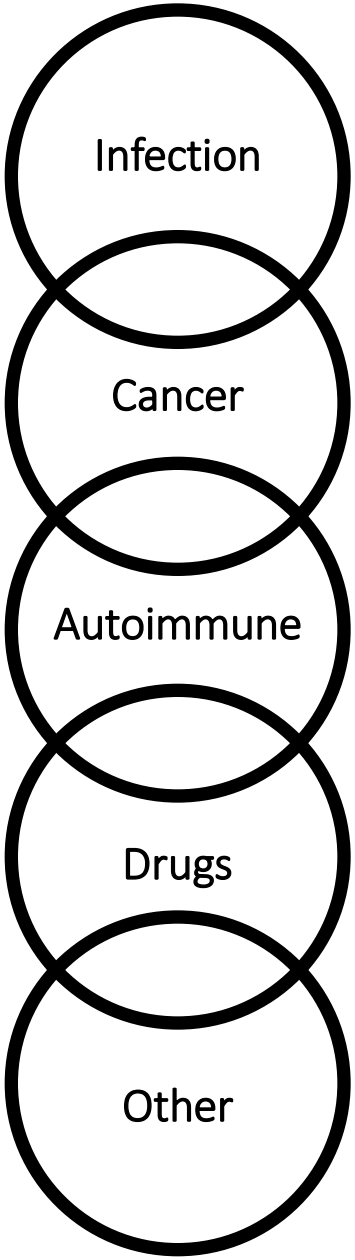
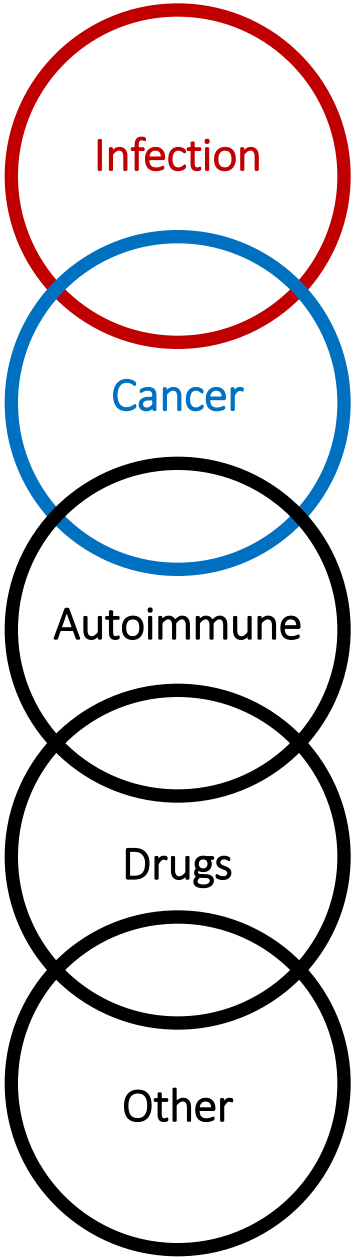
Common causes of FUO Unusual presentations of common diseases	
Infective causes (35%) **Infections** of one kind or another is a common cause of fever **Deep seated abscesses** (subphrenic, retroperitoneal spaces, liver or pelvis) **Previous abdominal operations or trauma,** **History of diverticulosis** **Diagnostic/therapeutic procedures** (endoscopy or gynecological procedures)	Non-infectious causes (65%) **Many illnesses** can trigger the release of fever-inducing pyrogens Fever can be seen in patients with **cancer hematologic malignancies, solid tumors** Certain **autoimmune conditions** are associated with intermittent fevers vasculitis, connective tissue diseases D**rugs** like Beta-lactam antibiotics, procainamide, isoniazid, alpha-methyldopa, quinidine, and phenytoin can cause



Common underlying causes of FUO by etiology	
Infections Bacterial: Endocarditis, abscesses, TB, etc. Viral: CMV, EBV, HIV, hepatitis Fungal: Histoplasmosis, cryptococcosis Parasitic: Malaria, leishmaniasis, toxoplasmosis	35%
Neoplasms Lymphomas (especially Hodgkin), leukemias Solid tumors with metastasis, renal cell carcinoma	25%
Non-infectious inflammatory disorders Collagen vascular disease, adult-onset Still's disease, SLE Vasculitides (Polyarteritis nodosa, Giant cell arteritis) Granulomatous diseases (Sarcoidosis, Crohn)	15%
Miscellaneous disease Drug fever, neurological disorders, factitious fever, Familial Mediterranean Fever	15%
Unknown cause	10%



Fever mechanism in infection

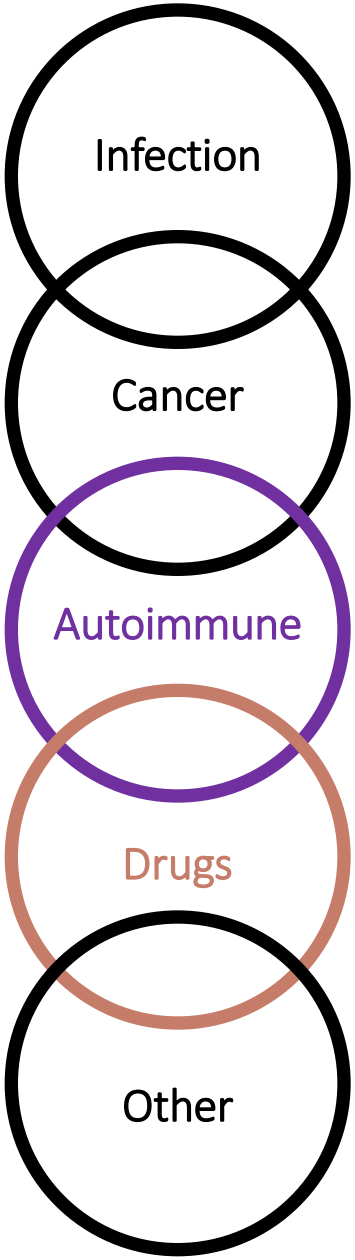
- Infection triggers immune response
- Immune cells release cytokines
- Cytokines signal hypothalamus
- PGE2 production increases
- Temperature set-point rises
- Body generates and conserves heat
- Fever develops as physiological response

localized by system:
sinusitis, dental abscess, endocarditis, tuberculosis, abdominal abscesses, hepatitis, pyelo, prostatitis, epididymitis, infectious arthritis, diskitis
generalized viral:
ebv, cmv, hsv, hiv
generalized fungal
zoonoses (us): anaplasmosis, babesiosis, brucellosis, ehrlichiosis, leptospirosis, lyme disease
zoonoses (global):
chikungunya, dengue, filariasis, kala azar, lassa fever, malaria, q fever, typhoid, zika

Fever mechanism in cancer

- Infection
- Tumor-related fever (Paraneoplastic phenomenon)
- Inflammation
- Other causes (DVT, PE, etc)

Organized by system
Heme:
Leukemia, lymphoma
Cardiac:
Atrial myxoma
Pulmonary:
Lung cancer, mesothelioma
GI:
Hepatocellular carcinoma, colon CA, Kaposi's sarcoma
Renal:
MM, RCC
Orthopedic:
Sarcoma, myelodysplastic syndromes



Fever in autoimmunity

Inflammation
Cytokine release
Cytokines signal hypothalamus
PGE2 production increases
Temperature set-point rises
Body generates and conserves heat
Fever development

Drug induced fever

Immune responses
Interference with thermoregulation
Direct pharmacological effects

aka noninfectious inflammatory or rheumatologic disease:

More common:
GCA, PAN, PMR, sarcoidosis, SLE

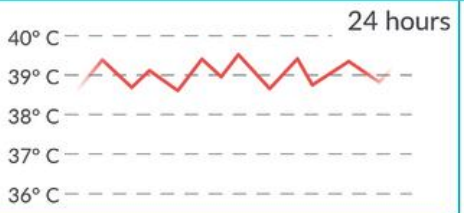
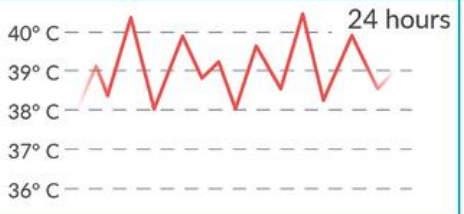
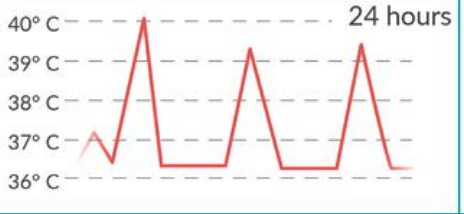
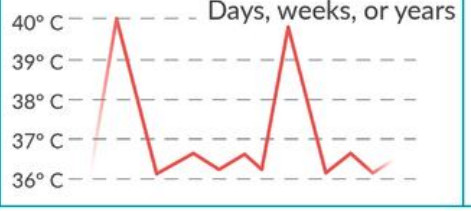
Less common:
Allergic granulomatosis angiitis, APS, aortitis, Behcet's, cryoglobulinemia, IBD, Reactive arthritis, Still's Disease Takayasu's arteritis, vasculitides

think anti....

Antimicrobials
especially sulfonamides, penicillins
Antiepileptics
Antithyroid
Anti-inflammatories

Impaired temperature regulation:
Neurologic or dermatologic
Environmental
Endocrine
ex. Thyroiditis
Factitious
VTE:
DVT, pulmonary emboli

Common underlying causes of FUO by site of disease
Cardiovascular Infective endocarditis, myocarditis, vasculitis
Respiratory Tuberculosis, empyema, lung abscess
Gastrointestinal Liver abscess, subphrenic abscess, IBD, cholangitis diverticulitis
Genitourinary Pyelonephritis, renal abscess, prostatitis
Osteoarticular Septic arthritis, Polymyalgia rheumatica
Hematologic/Lymphatic Lymphoma, leukemia, histiocytosis

Types of fever	Course	Examples of associated conditions
Continuous		• Viral and bacterial infections
Remittent		• Viral infections • Acute bacterial endocarditis
Intermittent		• Pyogenic, focal infections • Tuberculosis • Juvenile idiopathic arthritis
Undulant		• Brucellosis
Biphasic		• Dengue fever
Recurrent		• Tick-borne diseases (e.g., borreliosis) • Hodgkin lymphoma

Characteristics of Fever		
Fever Type	**Definition**	**Associated Conditions**
Intermittent fever	Fever that touches normal for a few hours during the day	Malaria, tuberculosis, typhoid, SLE, rheumatoid arthritis
Remittent fever	Fever that fluctuates >1.0^{0}C in 24 hours without touching normal	Pneumonia, endocarditis, brucellosis, typhoid
Continuous fever	Fever that does not touch normal and fluctuates less than 1.0^{0}C in a day	Enteric fever, bacterial endocarditis, viral pneumonia
Fever with rigors	Fever accompanied by severe shaking chills	Malaria, lobar pneumonia, cholangitis, pyelonephritis, bacterial endocarditis, abscess
Step ladder fever	Gradual stepwise increase in temperature	Enteric fever
Relapsing or periodic fever	Fever occurring in bouts lasting for days with afebrile phases	Brucellosis, Hodgkin lymphoma
Sudden onset fever	Rapid elevation in body temperature, often within a few hours	Pyelonephritis, pneumonia.
Gradual onset fever	Body temperature increases slowly over time, often low-grade and subacute	Typhoid, IE, TB, Brucellosis
Double rise of fever	Temperature rises and falls twice within a 24-hour period	Malaria, liver abscess, typhoid, UTI, Kala-azar

FUO Types Durack & Street, 1991	
Classic	Patients who meet the original criteria of FUO, with a new emphasis on the **ambulatory evaluation** of these previously healthy patients Common causes are **infection, malignancy, and collagen vascular disease, etc**
Nosocomial	Fever on several occasions in a hospitalized patient for **at least 24 hours without an obvious source of infection** that could have been present before admission. Minimum of **three days of evaluation** without establishing the cause is required Causes include **septic thrombophlebitis, pulmonary embolism, *Clostridium difficile* enterocolitis, drug-induced fever and infections in intubated patients**
Neutropenic	Recurrent fever with neutrophil count of **<500 per mm^3** and who has been **assessed for three days without establishing an aetiology** for the fever. Causes include **opportunistic bacterial infections or systemic fungal infection**
HIV-Associated	Recurrent fevers over a **4 week** period in an outpatient or for **3 days in a hospitalized patient with HIV infection.** HIV makes patients susceptible to **opportunistic infections** (*Mycobacterium avium-intracellulare* complex, *Pneumocystis jirovecii* pneumonia and cytomegalovirus) **Non-infectious causes** include **lymphomas, Kaposi's sarcoma and drug-induced fever**

Neoplastic fever criteria

- **Temperature** >37.8°C (100.04°F) at least once a day
- **Duration** of fever >2 weeks
- **Lack of evidence of infection** (physical examination, laboratory examinations and imaging studies)
- **Absence of allergic mechanisms** (drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction)
- **Lack of response** to empiric adequate antibiotic therapy for at least 7 days
- **Prompt lysis of fever by the** Naproxen test with sustained normal temperature while receiving Naproxen

Mechanisms of neoplastic Fever

Mechanisms are not fully understood but can be caused

I**nfection, tumor-related pyrogenic substances, inflammation, or drug-induced reactions**

Release of pyrogenic cytokines either directly from **tumour cells or from macrophages** responding to tumour are likely to play a major role

Drug-induced fever

Coagulation disorder and pulmonary embolism

No pathognomonic fever pattern cancer

Naproxen test

Cancer fever has steadily declined from **19% in 1961 to 7% in 2007 as a cause of FUO**

Causes of fever in cancer

1. **Infection:**

   Cancer treatments, particularly chemotherapy, can cause **neutropenia**, increasing the risk of **infection**.

2. **Tumor-related fever (Paraneoplastic phenomenon):**

   Some tumors **(RCC, lymphomas, myelogenous leukemias)** can directly produce pyrogenic cytokines (**IL-1, IL-6, TNF-α and INF-γ)** which can raise body temperature.

3. **Inflammation:**

   Inflammation (tumor growth or cancer treatments related) releases cytokines can raise the hypothalamic set point and contribute to fever.

4. **Other causes:**

   DVT, PE, etc

Drug-induced fever	
Hypersensitivity reactions	Drugs or its metabolite trigger immune response with **Ag-Ab complex** formation, T cell activation, **cytokine release** and **hypothalamic stimulation**, leading to **fever, rash, altered LFTs, eosinophilia** or even **DRESS Syndrome**
Altered thermoregulation	Some drugs (anticholenergics) can interfere with the body's ability to dissipate heat by **reduce sweating** Other drugs (sympathomimetics) can **increase metabolic rate**, leading to **higher heat production**
Pharmacological effects	Some drugs (**chemotherapeutic agents**) may cause fever as a direct consequence of their **pharmacological action**
Idiosyncratic reactions	Rare unpredictable reaction due to **genetic predisposition** (haloperidol or sulfonamides)
Drug administration related	Fever after injection or infusion, due to **pyrogenic contaminants** in the drug product or phlebitis or after receiving vaccines

Factitious fever

Responsible for as many as **10% of FUO cases**

Most commonly encountered among **young adults with health care experience or knowledge**

Evidence of **psychiatric problems or a history of multiple hospitalisation**

Rapid changes in oral temperature without associated shivering or sweating Large differences between rectal and oral temperature

Discrepancies between fever, pulse rate, or general appearance

Fever may be caused by **injection of non-sterile material** (feces, milk), resulting in **atypically localized abscesses or polymicrobial infections**

Special patient populations

Elderly Patients

- Blunted fever response
- Atypical presentations common
- Lower threshold for investigation
- Endocarditis, malignancy, mycobacterial infection

Immunocompromised Patients

- Expanded differential diagnosis
- Opportunistic infections predominate
- Lower threshold for early empiric therapy
- Mycobacterial infection, fungal infection, CMV

Diagnostic approach: initial evaluation

History

- Pattern and duration of fever
- Associated symptoms
- **Travel history**
- Occupational exposures
- Medication history
- Risk factors (immunosuppression, IV drug use)

Physical Examination

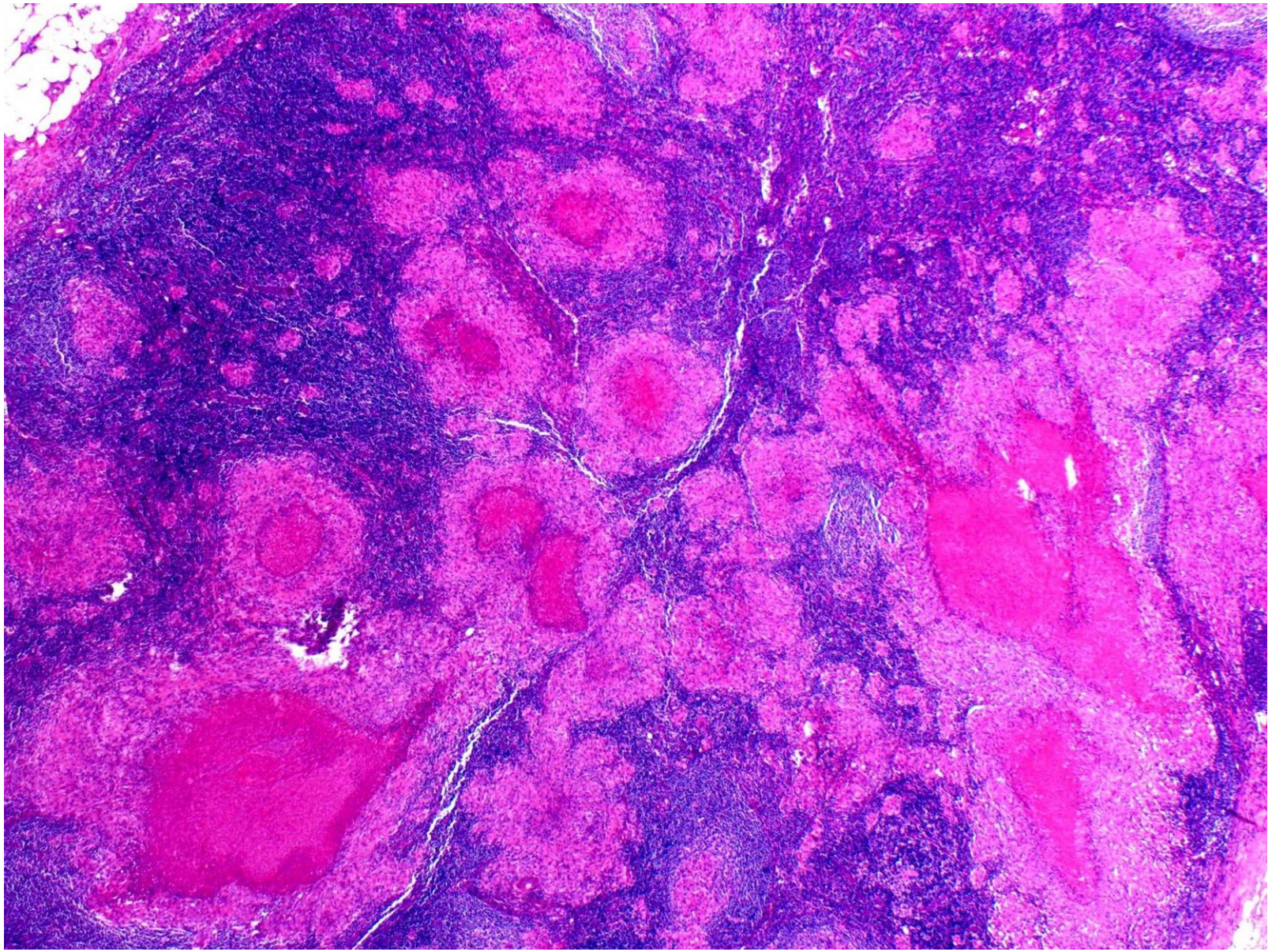
- Skin lesions
- Lymphadenopathy
- Heart murmurs
- Abdominal tenderness
- Joint examination

Diagnostic Approach		
First-line Investigations	Second-line Investigations	Advanced techniques
Basic Laboratory Tests Complete blood count with differential **(CBC)** Comprehensive metabolic panel **(CMP)** Inflammatory markers **(ESR, CRP)** **Blood cultures** (3 sets, before antibiotics) **Urinalysis and urine culture** **Chest X-ray** Tuberculin skin test or Interferon-Gamma Release Assay (IGRA) **Initial Imaging** Chest radiography Abdominal ultrasound	**Advanced Imaging** CT scan (chest, abdomen, pelvis) MRI for specific areas of concern Echocardiography Other tests **Specific Tests** Serological studies for specific infections Autoimmune panels Bone marrow examination Tissue biopsies	**Molecular Diagnostics** PCR-based pathogen detection Next-generation sequencing (NGS) Metagenomics (Microbial genomic analysis) **Nuclear Medicine** 18F-FDG PET/CT scan High sensitivity for infections, inflammation, malignancy Can guide biopsy sites Particularly useful when other studies are negative
Start with basic non-invasive investigation **The value of a test depends on the pretest probability of the disease**		

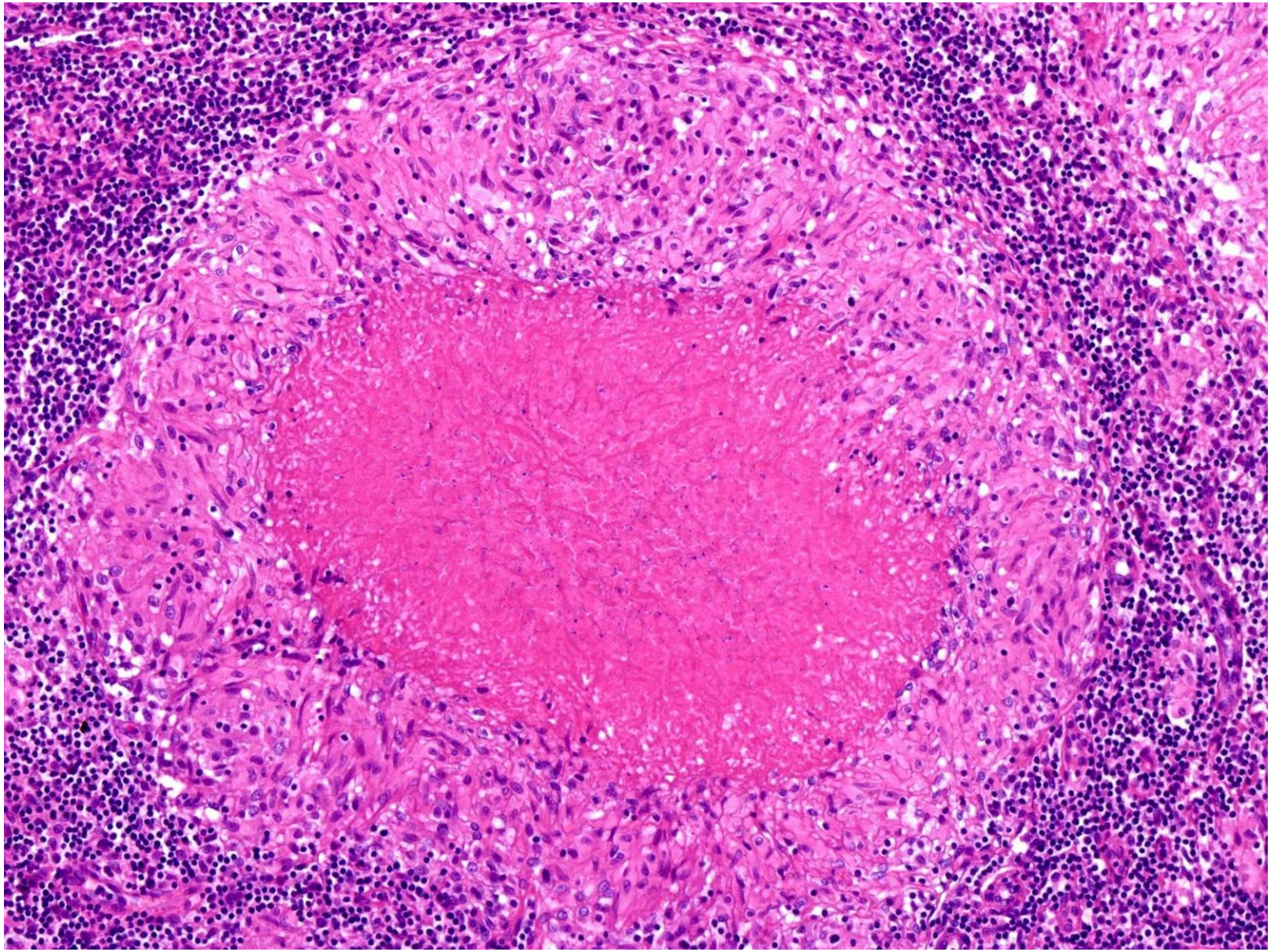
Diagnostic Imaging in Patients with FUO	
Imaging	Possible diagnoses
Chest radiograph	Tuberculosis, malignancy, *Pneumocystis jerovecii* pneumonia
CT of abdomen or pelvis with contrast	Abscess, malignancy
Gallium 67 scan	Infection, malignancy
Indium-labeled leukocytes	Occult septicemia
Technetium Tc 99m	Acute infection and inflammation of bones and soft tissue
MRI of brain	Malignancy, autoimmune conditions
PET scan	Malignancy, inflammation
Echocardiography	Bacterial endocarditis
Venous Doppler study	Venous thrombosis

Management Principles		
General Approach	Specific Therapy	Symptomatic Management
Treatment directed at underlying cause **Avoid empiric antibiotics without clear indication** **Symptomatic management while investigating**	Infections: Appropriate antimicrobials Neoplasms: Chemotherapy, radiation, surgery Inflammatory disorders: Corticosteroids, immunomodulators Miscellaneous: Discontinuation of offending drugs, etc.	**Supportive Measures** Hydration Rest Nutritional support **Pharmacologic** Antipyretics (acetaminophen, NSAIDs) Relieve symptoms but may mask fever pattern Use judiciously during diagnostic workup

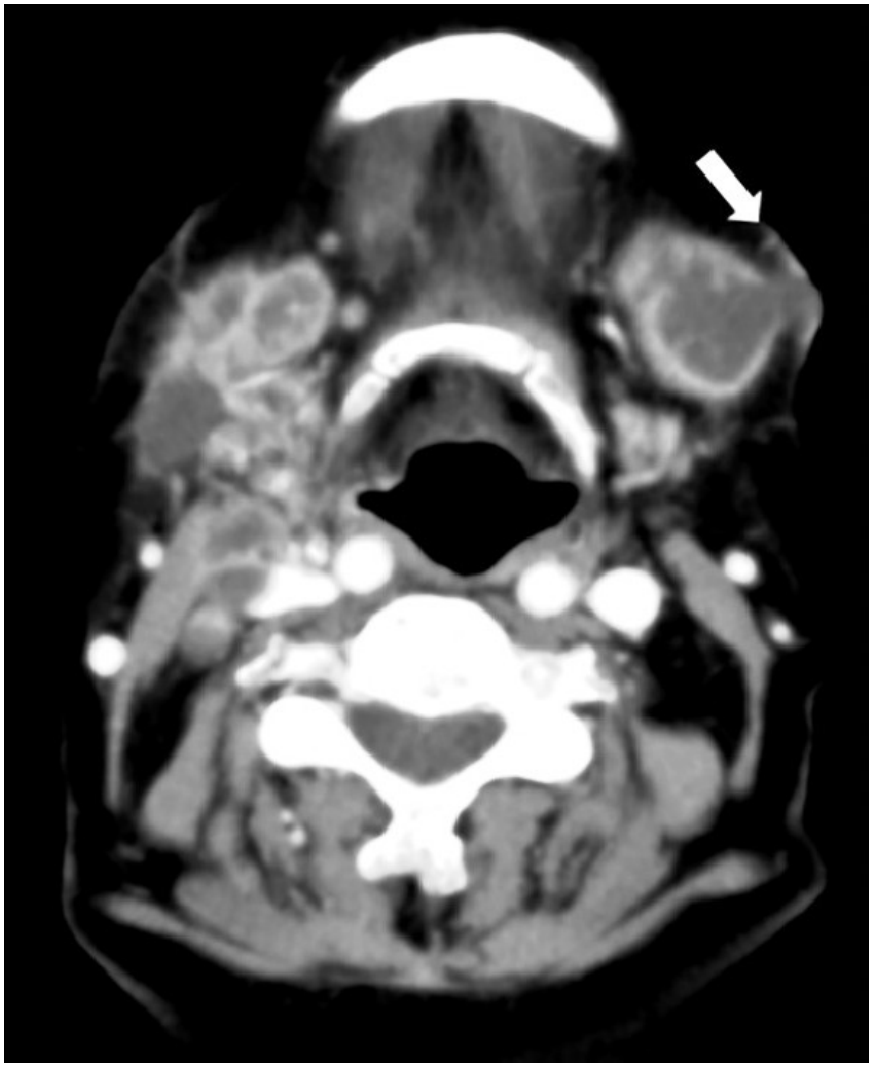
Examples

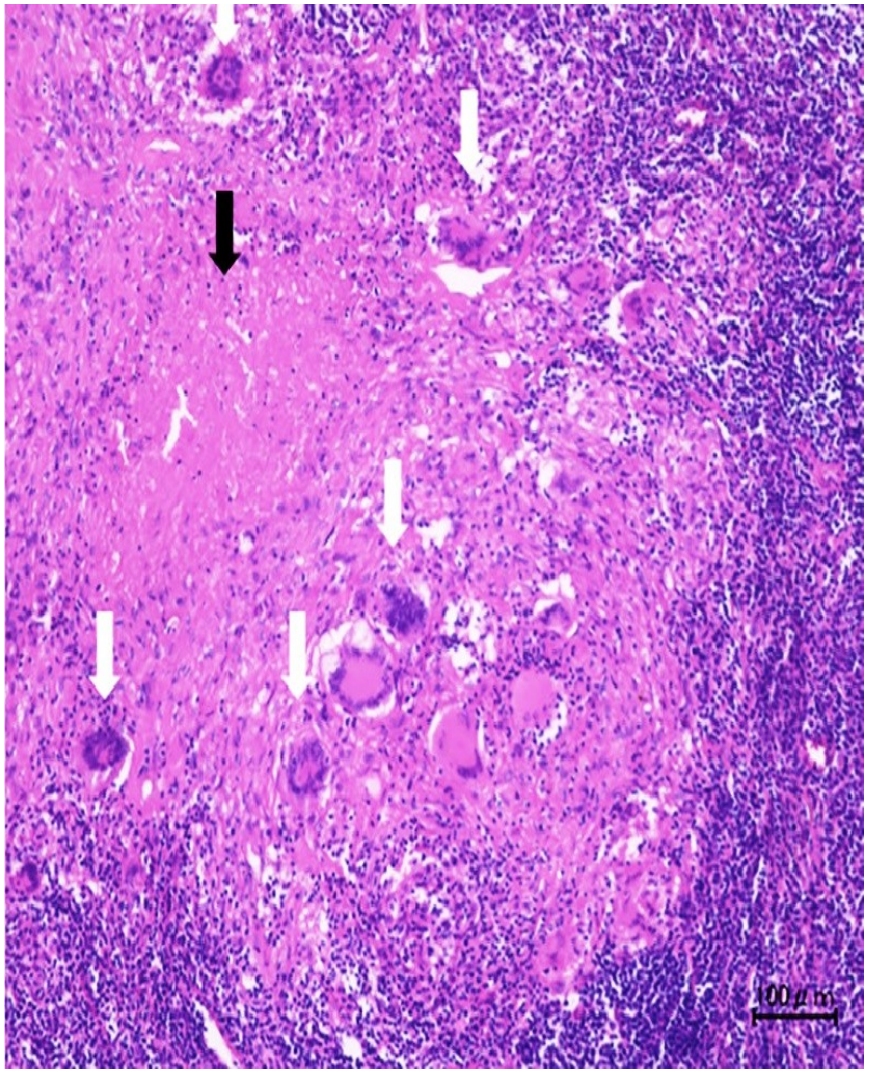


Caseating granulomatous (Bovine Mycobacterial lymphadenitis

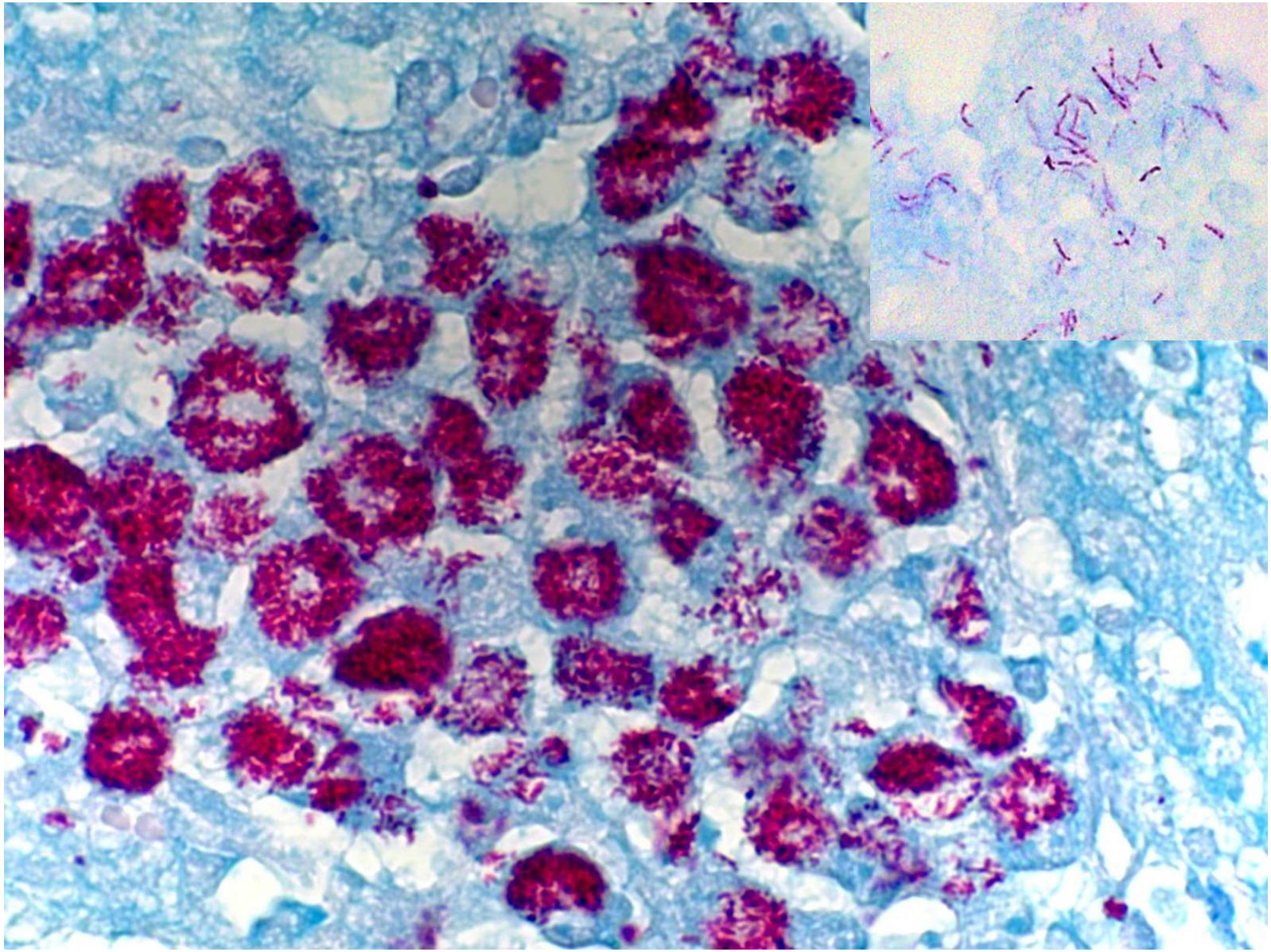


Caseating granulomatous (Bovine Mycobacterial lymphadenitis)



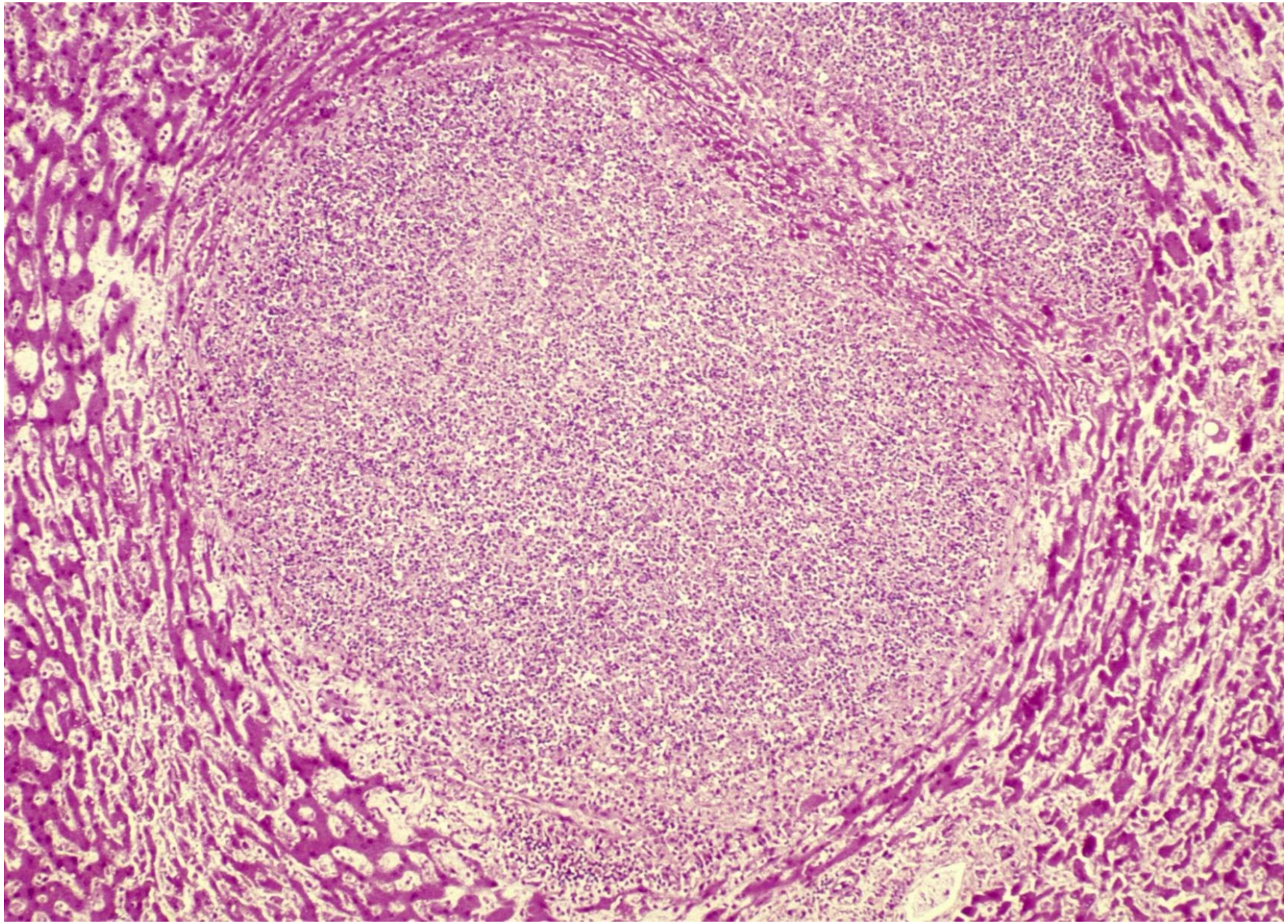


Necrotizing granulomatous lymph adenitis by MAIC

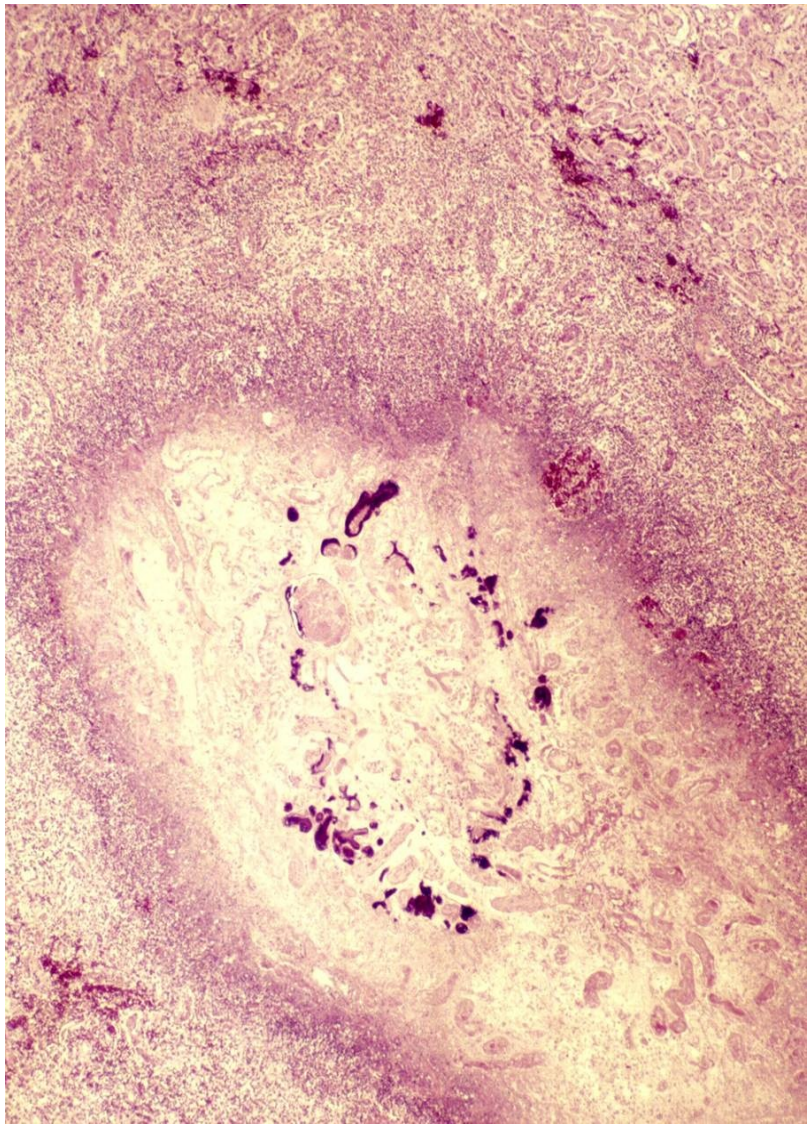


Acid fast bacilli in a ZN stained section from a case of MAI complex infection (HIV/AIDS setting)

Liver abscess (upper) and metastatic carcinoma (lower)

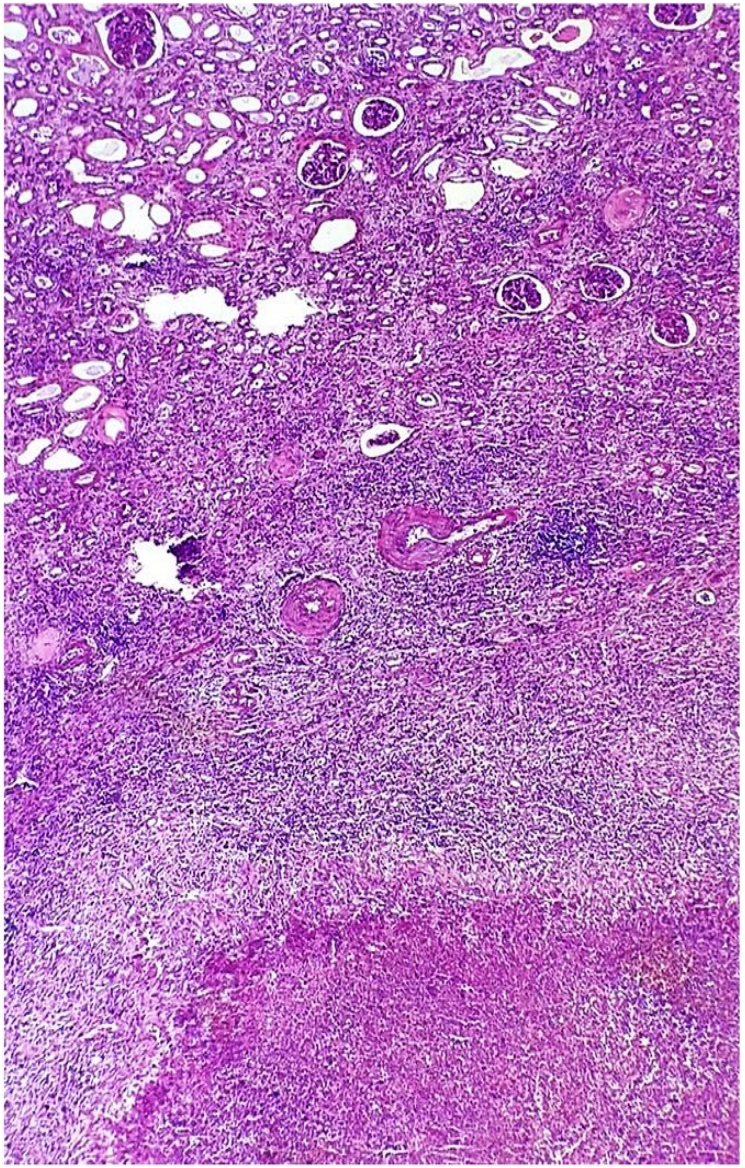


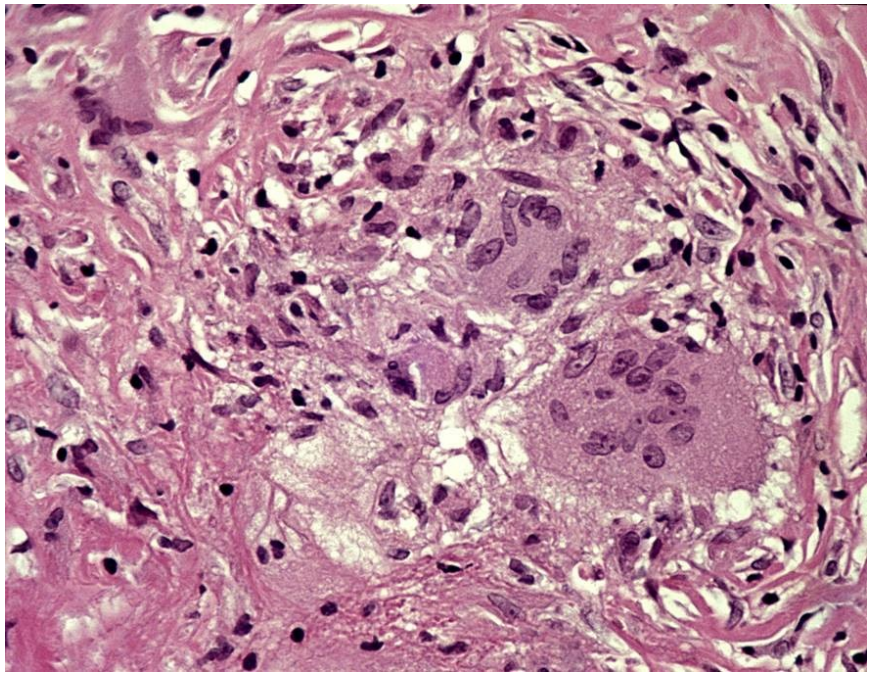
Liver abscess histology from the previous case



Renal abscess gross specimen (left) and histology (right)

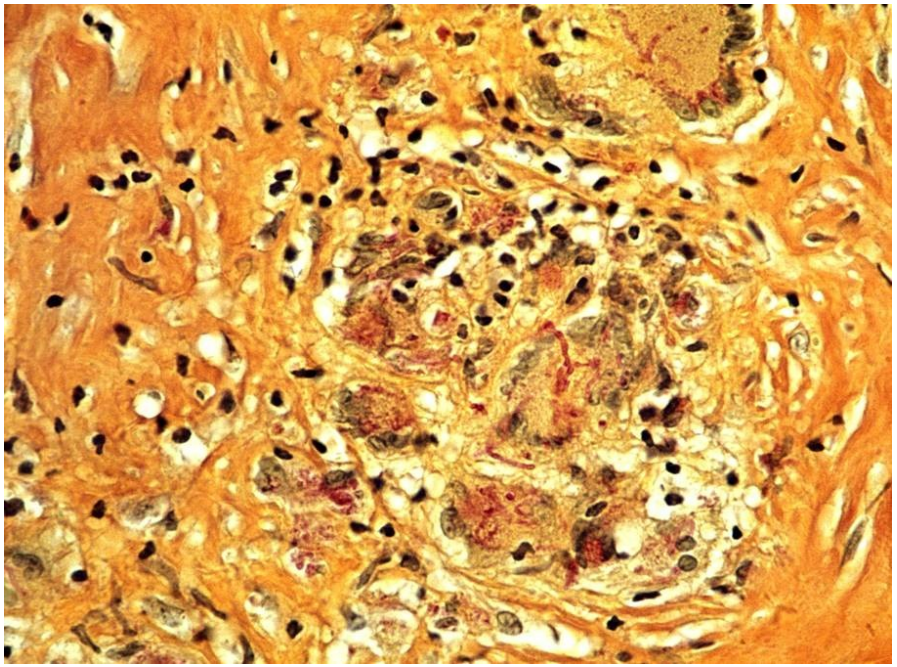
Renal tuberculosis

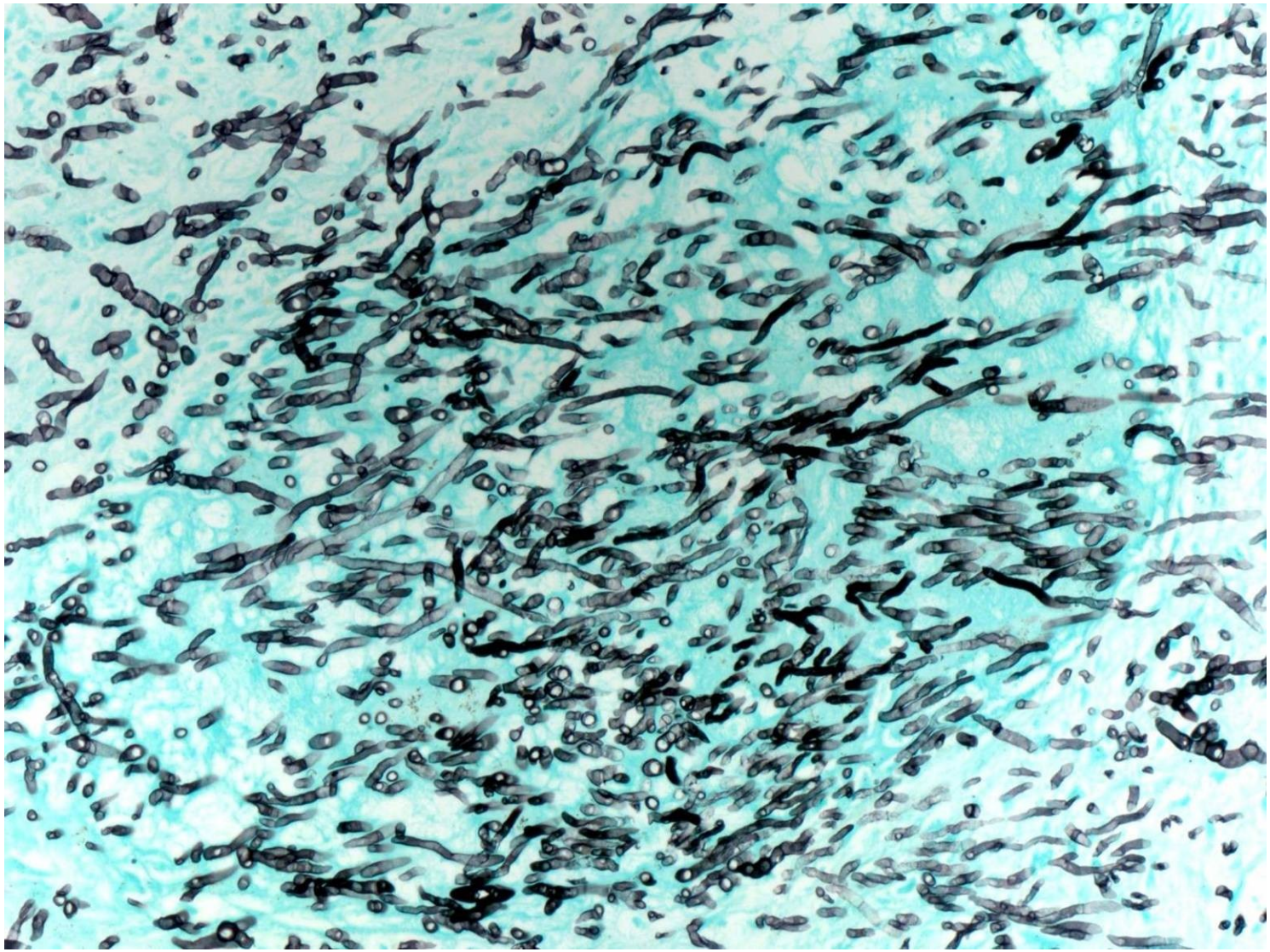




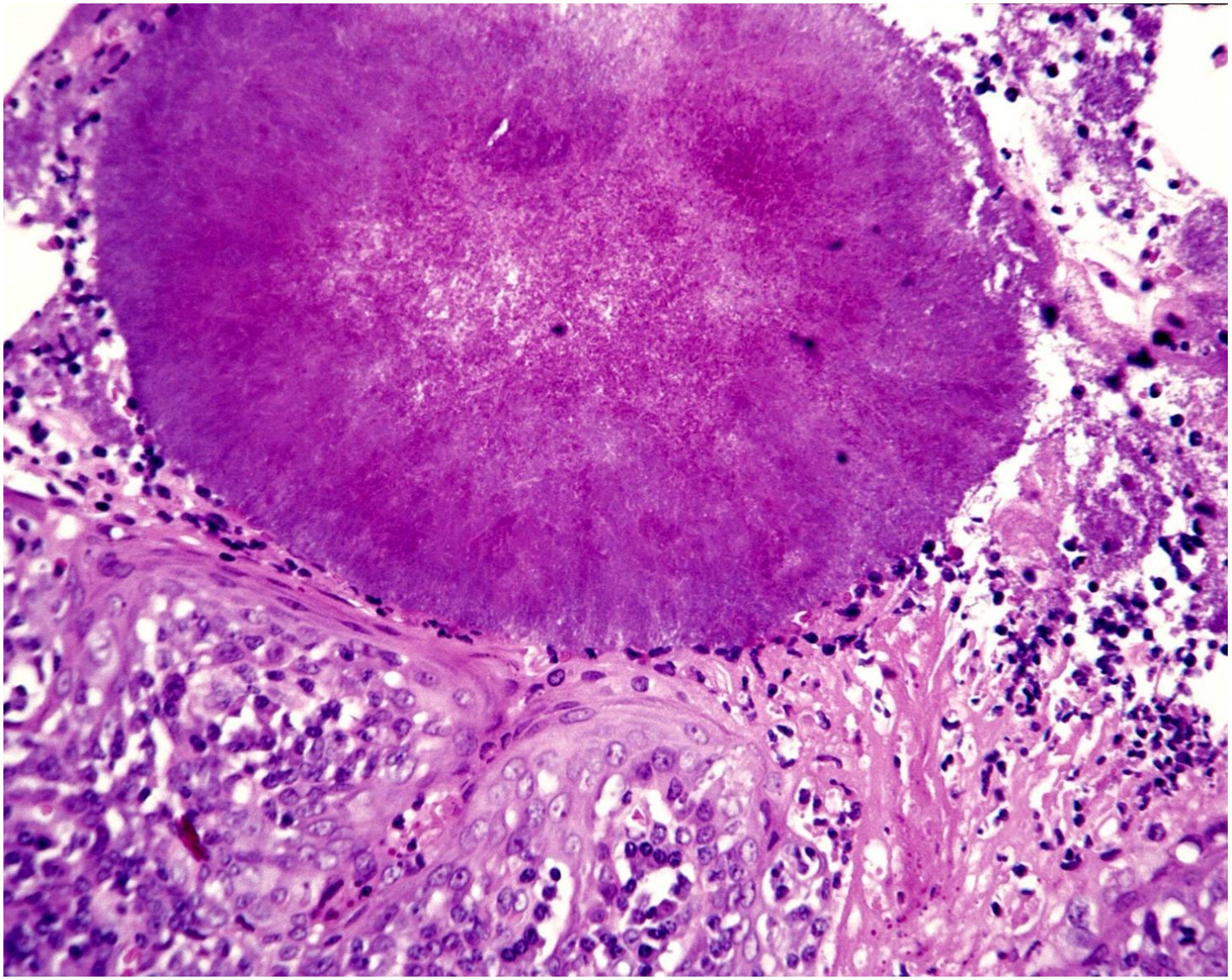
Fungal granulomatous sinusitis

Granulomas with multinucleated giant cells and eosinophilic fungal elements (right)

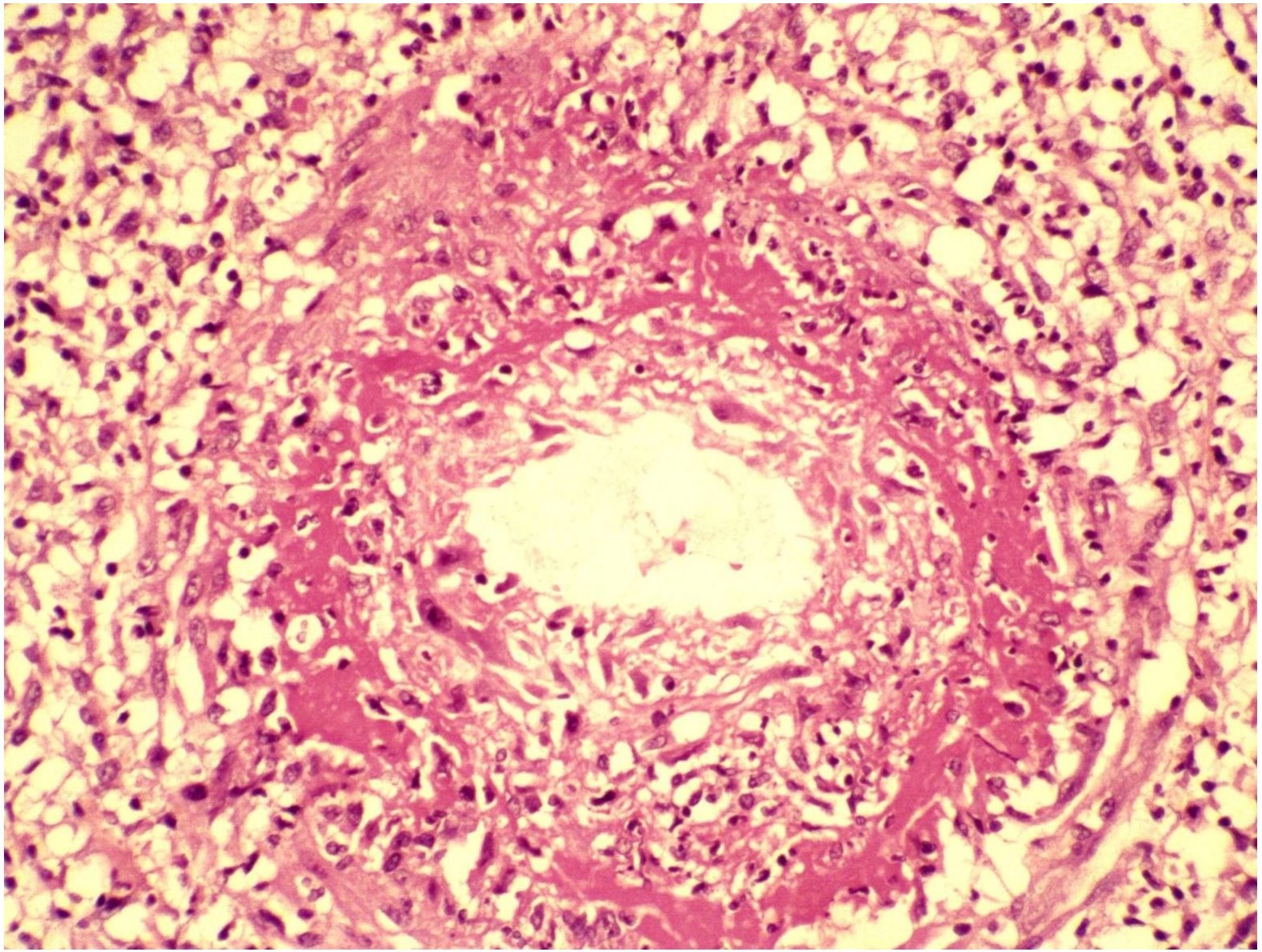




Aspergillus species in a lung abscess from an immunocompromised patient

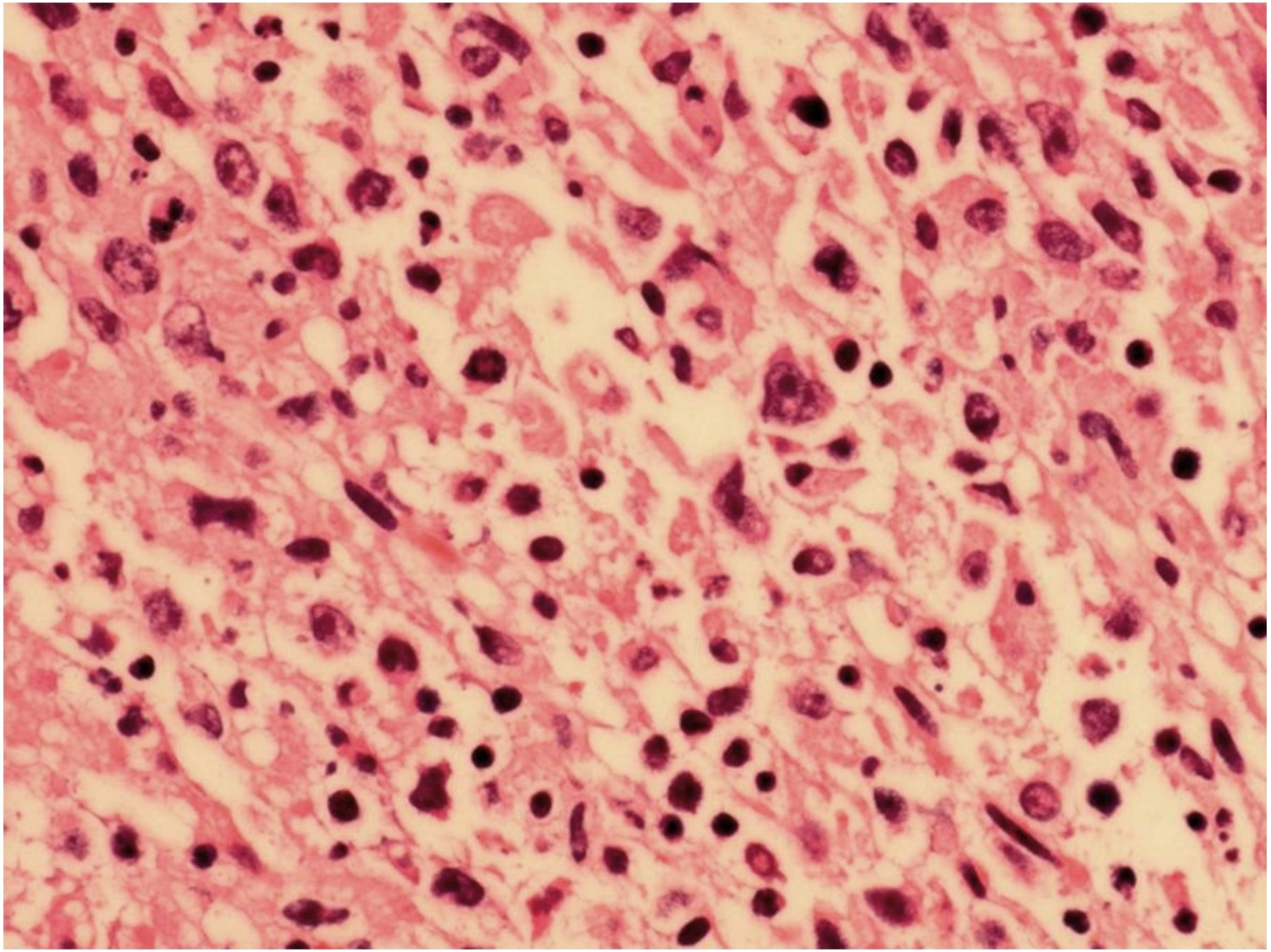


Actinomyces species in pelvic inflammatory disease



Necrotizing vasculitis from a patient with polyarteritis nodosa

Lymphoma of the spleen

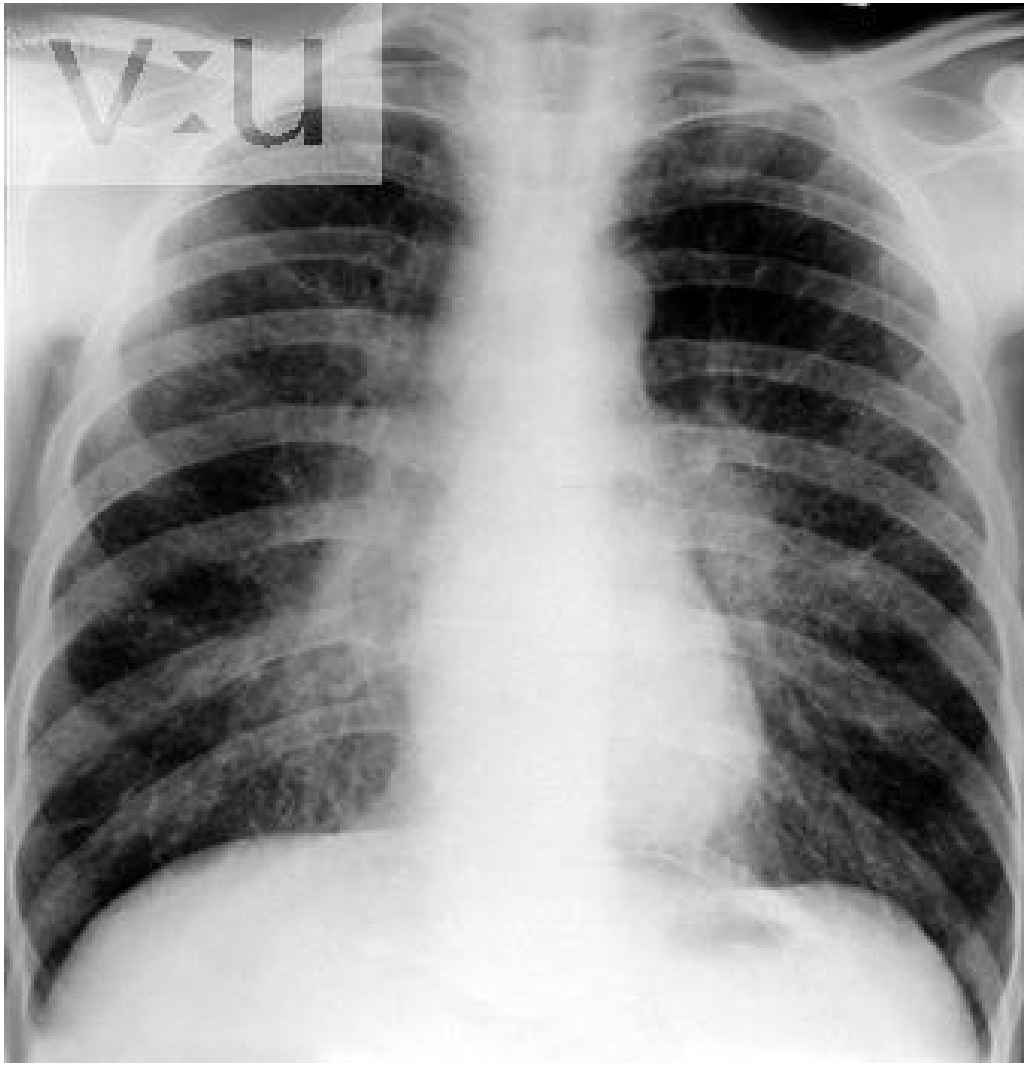


T-cell lymphoma of the small bowel of the enteropathy type

Case Presentation

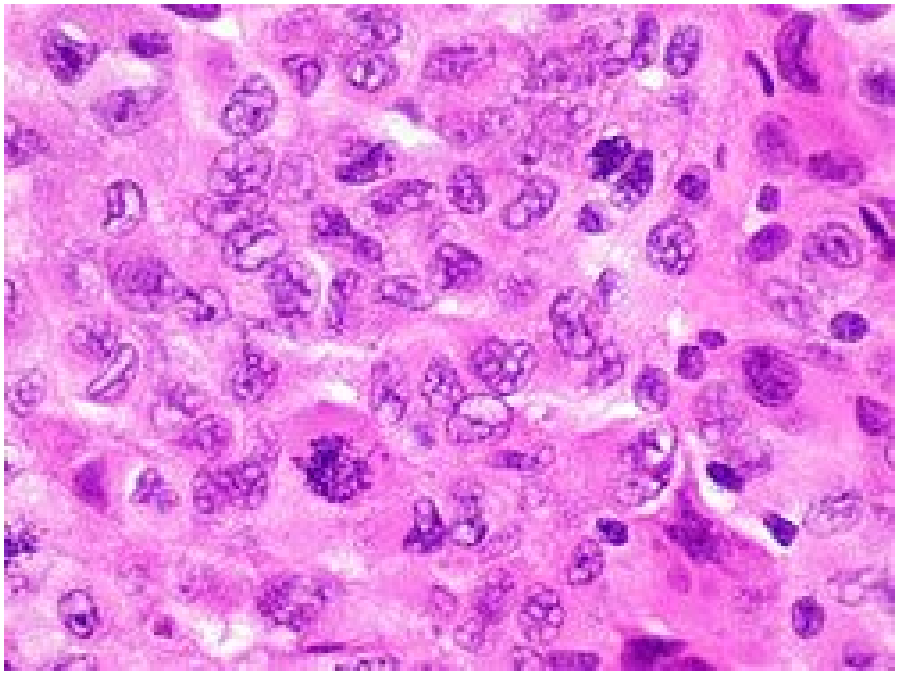
Case 1	
65 male Past 6 month 15kg weight loss Diarrhoea Dry persistent cough **Daily high fevers to 104F (40C)** Previously well No new medications	**FBC** Hb 10.5g/dL Platelets 550 WCC 9.0 **LFTs** ALP 150 ALT 60 GGT 300 AST 60 Inflammatory makers CRP 150 ESR 100

CXR



CT Abdomen

HiSpeed CT/i SYS#UAB3
A 165
UNIV. OF ALA. HOSP.BHAM
Ex: 4385
Se: 2
XY 1274.0
In: 45+C
67
Aug 14 97
512
MF:1.1
DFOV 36.0cm
STND
R
165
L
163
kV 120
mA 270
Large
7.0 mm/1.5:1
Tilt : 0.0
1.0 s/HE 10:17:54 AM/05.33
W:400 L:50
P 163

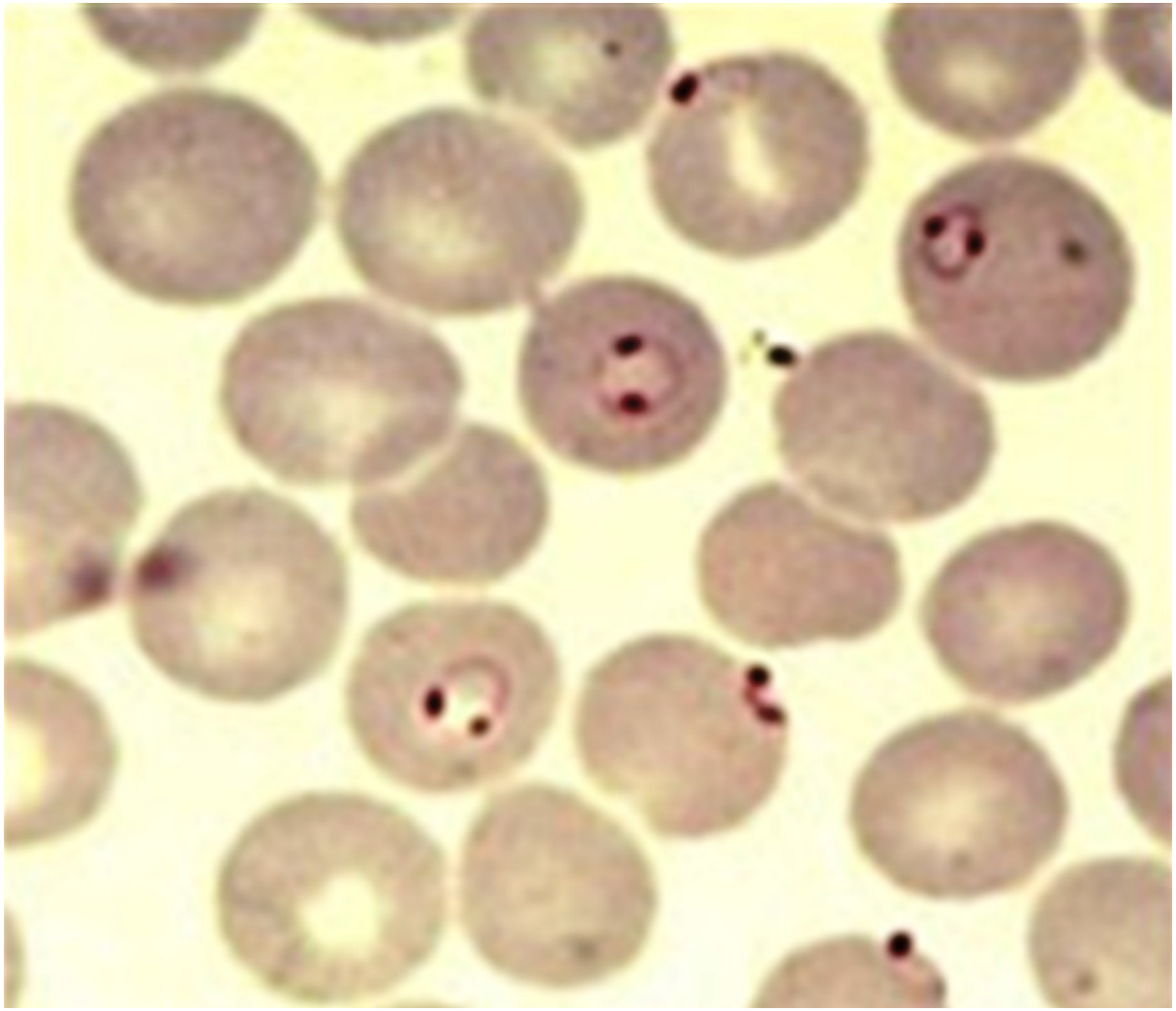


Metastatic Carcinoma of Unknown Primary (CUP) in the liver

Case 2	
25yo female Very unwell for **4 days** **Headache** **High fevers** **Diarrhoea** Aching all over Pale and mildly **jaundiced**	FBC Hb 7.0g/dL Platelets 50 WCC 2.0 Elects and LFT **Creatintine 250 (2.8)** LDH 500 AST 100 ALT 150 ALP 40 Bilirubin 90 (5.2)
Stool Results: No WCC, Occasional RBC, No growth	

CT Head

Blood Film

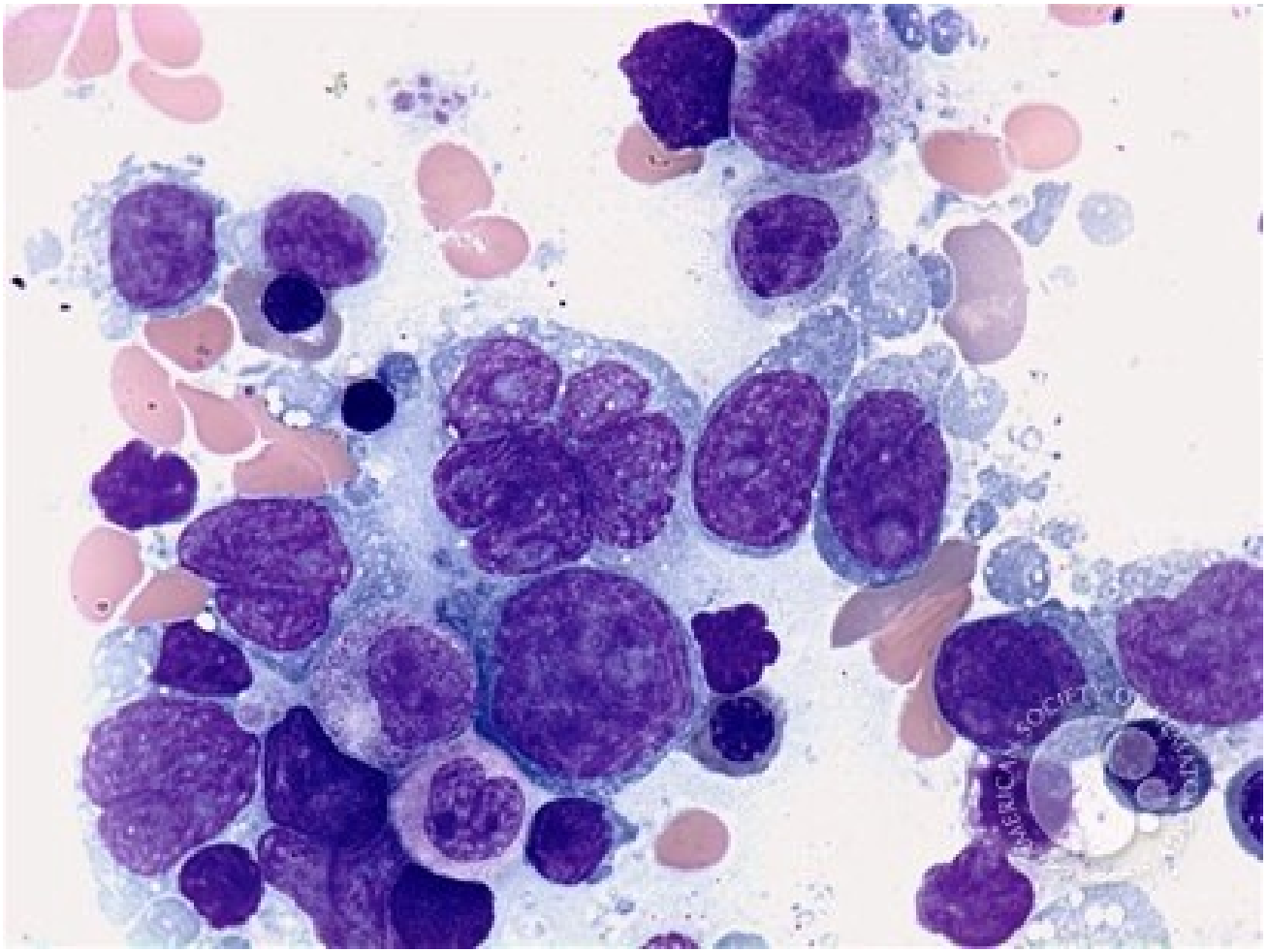


Plasmodium Falciparum

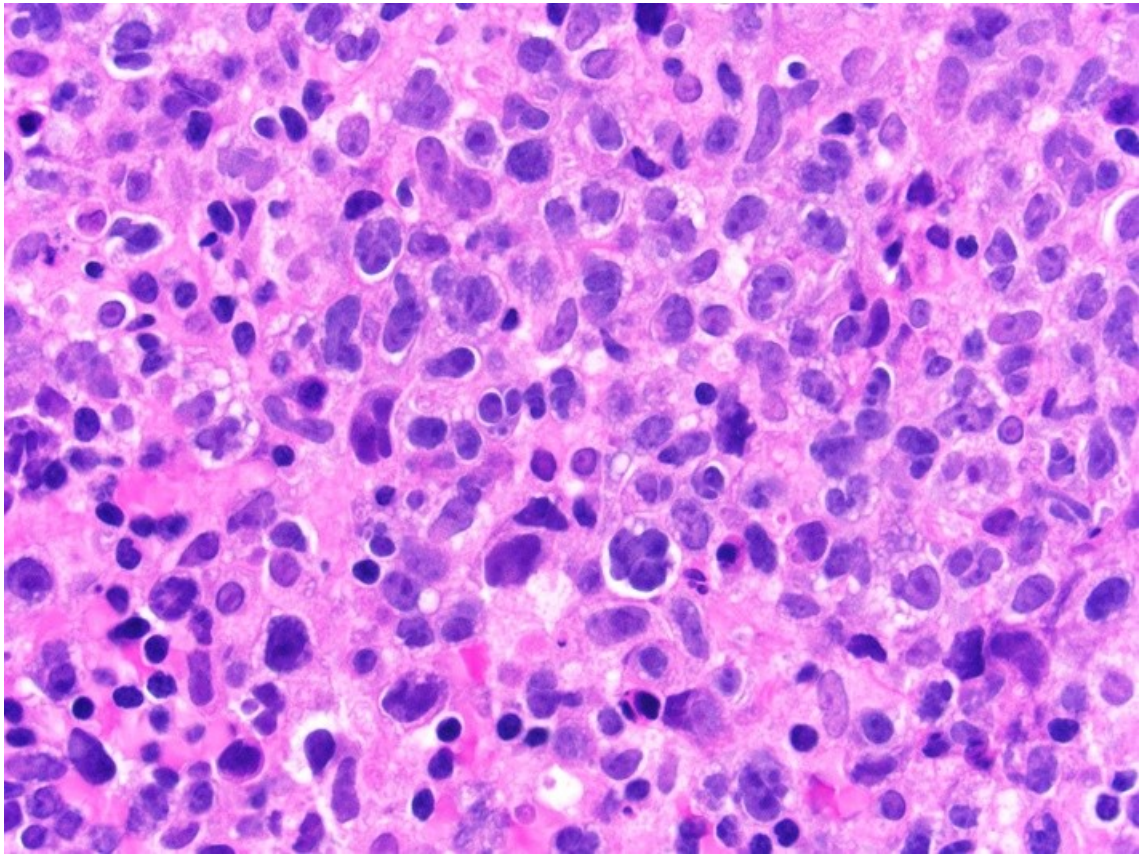
Cerebral Malaria

Case 3	
35 year old male Unwell **3 weeks** **Night fevers and sweats** Progressive **SOB** **Abdominal tenderness** Progressive pallor	FBC Hb 10 g/dL Plat 100 WCC 3.5 LDH 1200 LFT Normal Inflammatory markers **CRP 90** **ESR 90**
Bone marrow and lymph node biopsy	

Bone marrow



Lymph Node Biopsy

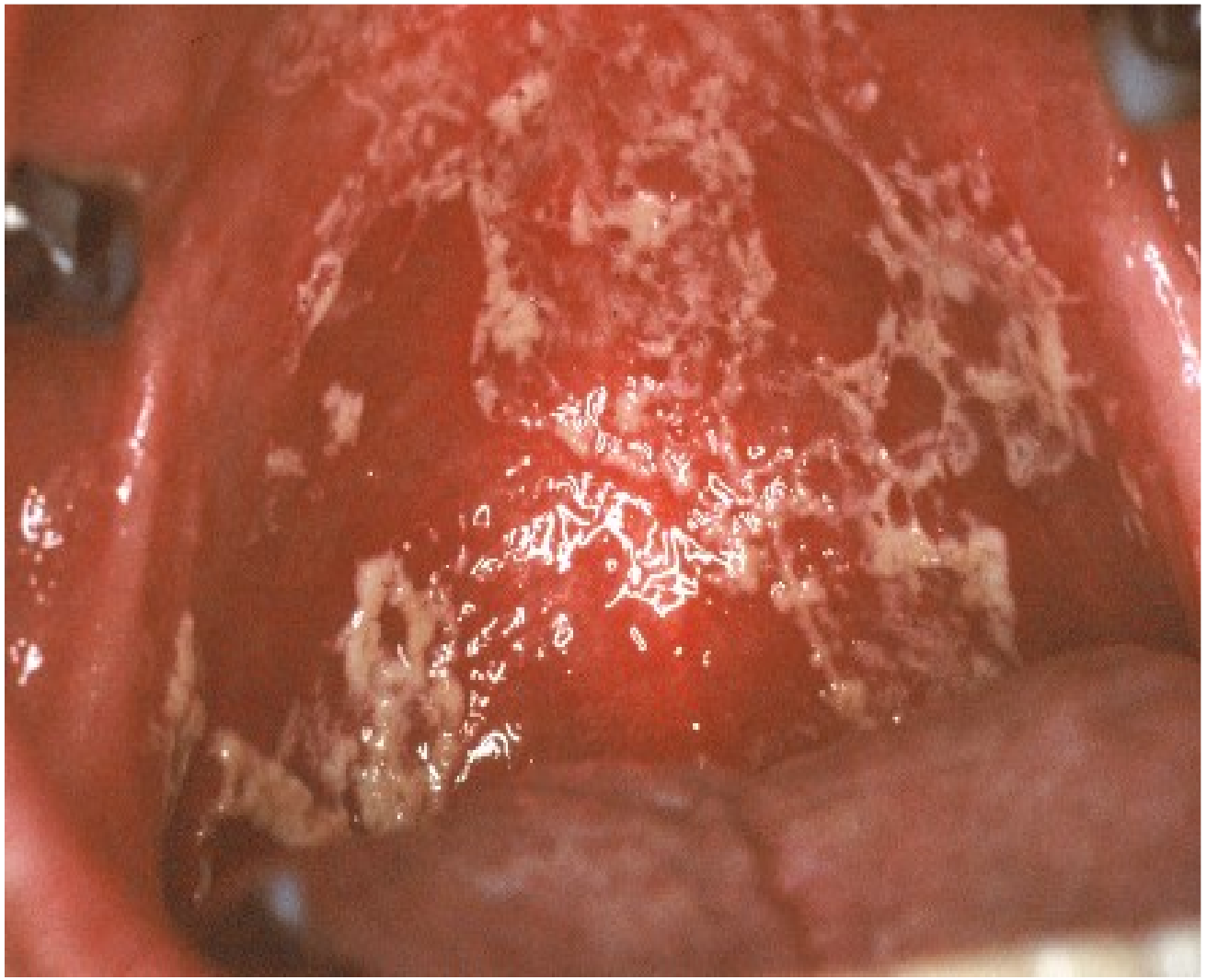


Non–Hodgkin Lymphoma

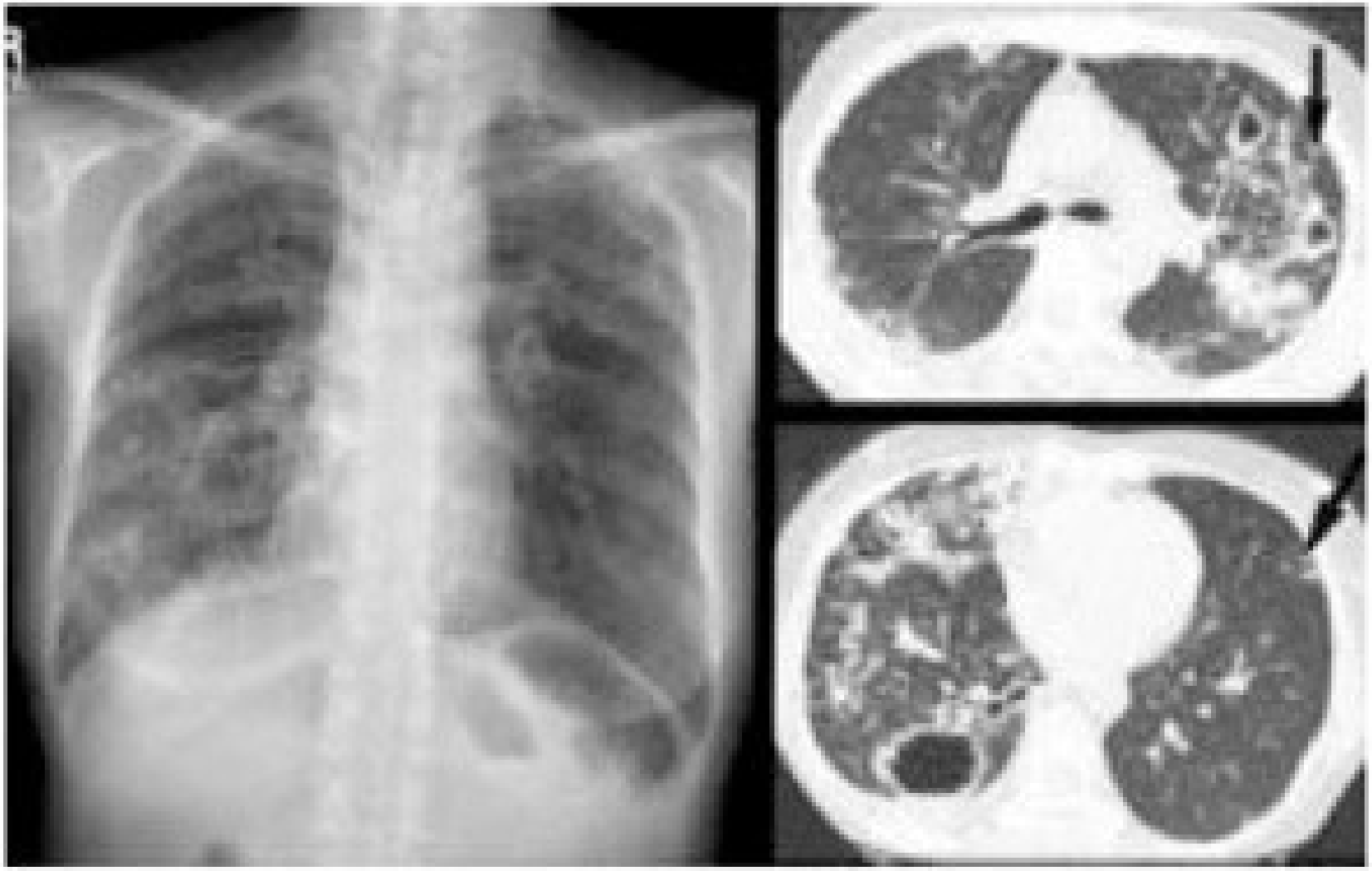
Diffuse large B Cell Lymphoma

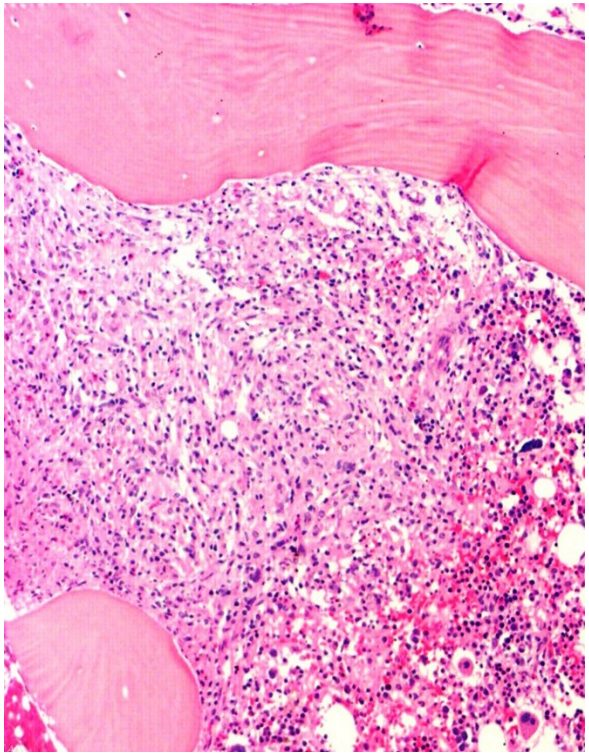
Case 4	
40yo male **HIV positive** Not on any medication **3 months** unwell **Weight loss and fevers** **Diarrhoea and sore mouth** No cough Very weak	Stool No RBC or WCC No Cysts, Ova, Parasites Blood Hb 8, WC 3, Plat 50 ESR 100, CRP 100
Bone marrow biopsy	

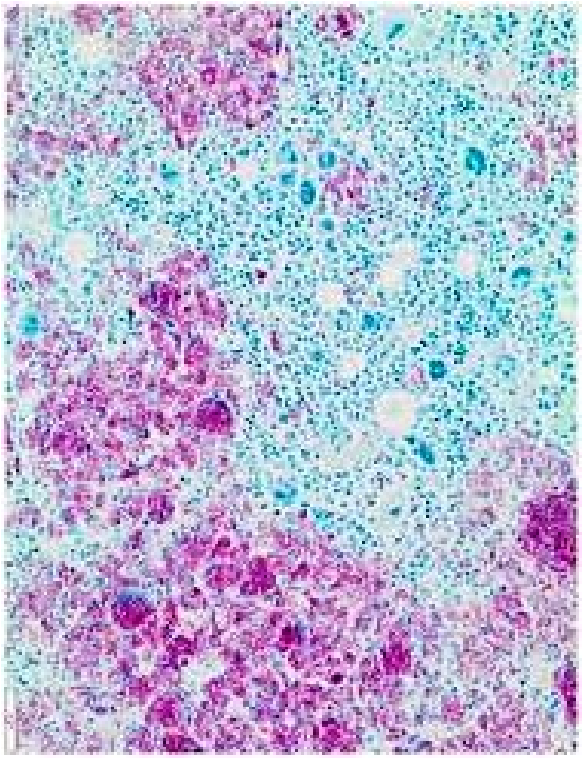
Oral Cavity

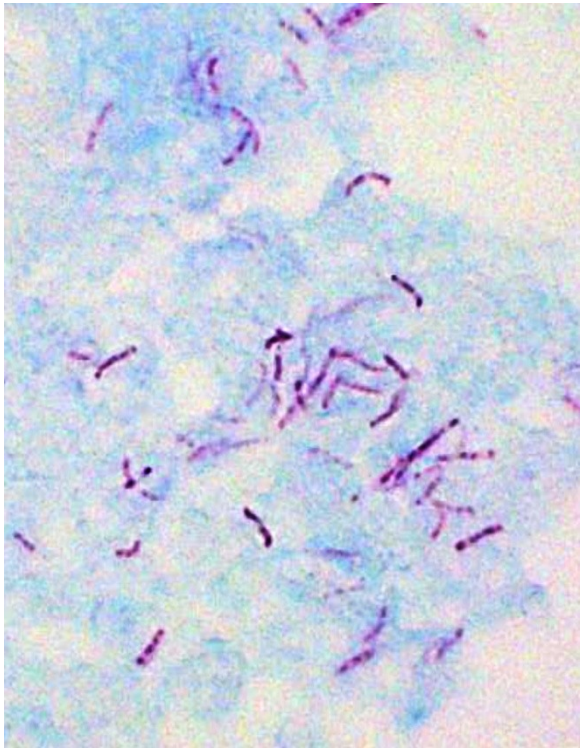


CXR-CT

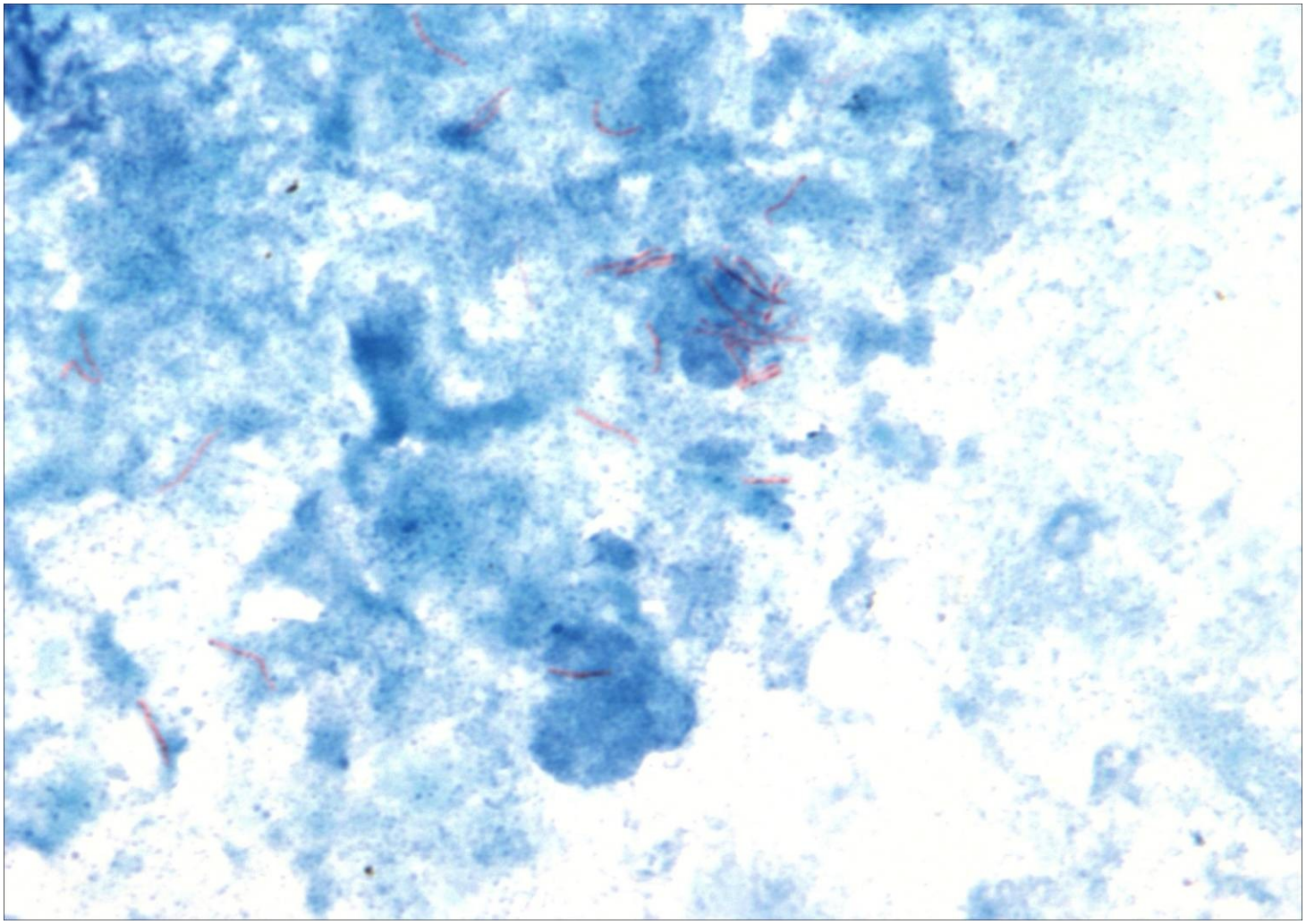






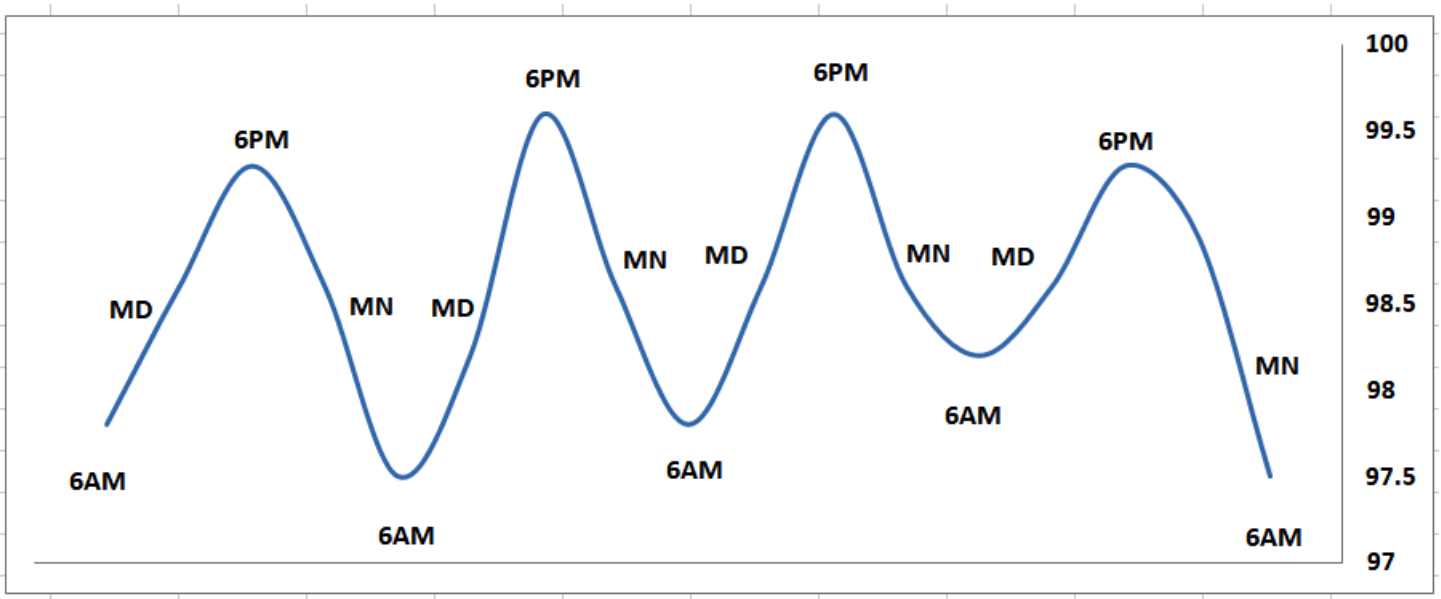


Bone Marrow, Blood, Stool, Sputum



Mycobacterium avium complex

Case 5	
23yo female university student “Fever” for six months Extensive Investigations: negative No weight loss Numerous medications not helping	ESR 3, CRP 2 FBC - Normal CMP - Normal
Temperature chart….	

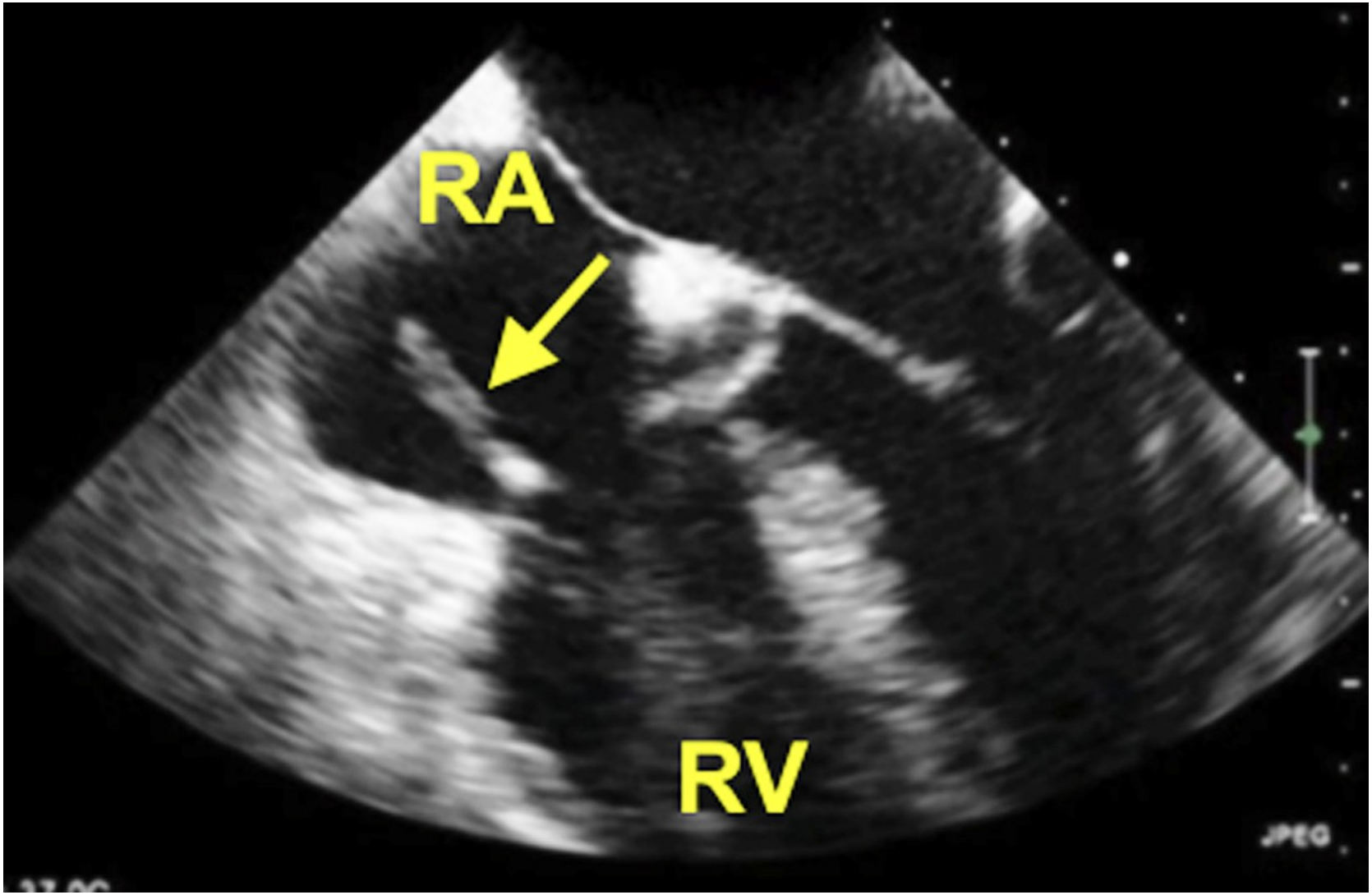


Normal

Case 6	
50yo female farmer Fever **3 weeks** Increasing SOBOE Rheumatic fever as a child	**Blood cultures** –negative x4 FBC Hb 10.5g/dL Platelets 600 WCC 7.0 Inflammatory markers CRP 120

Hands

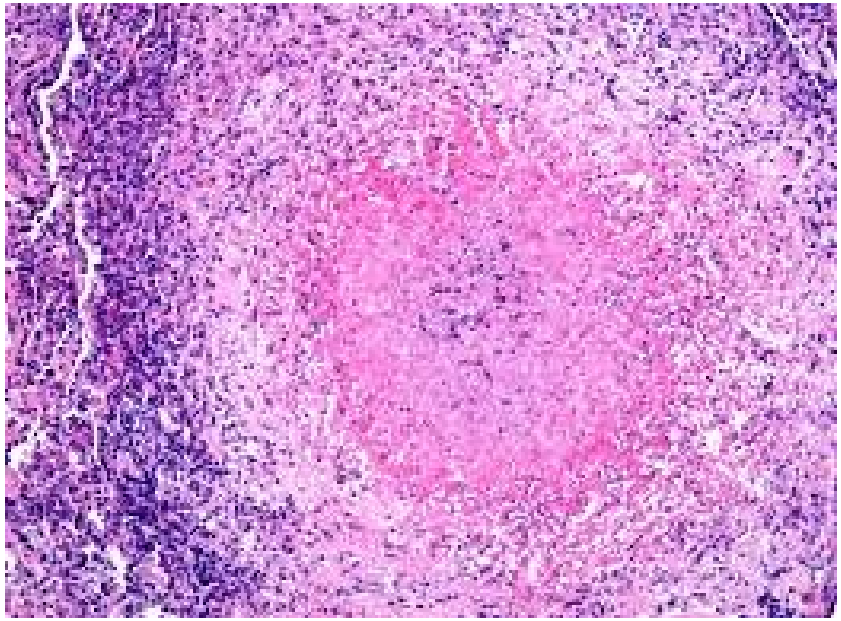
Echocardiography



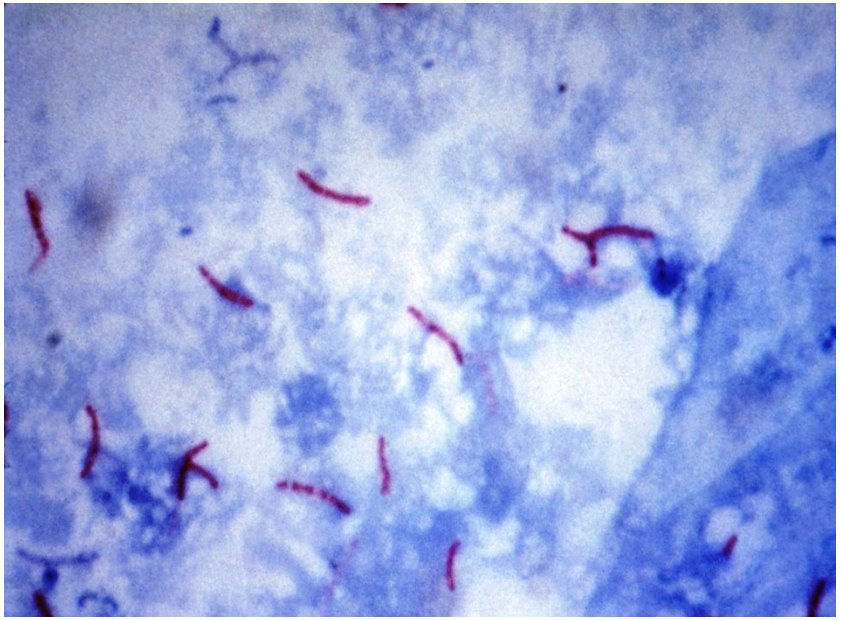
Culture negative endocarditis

Additional material

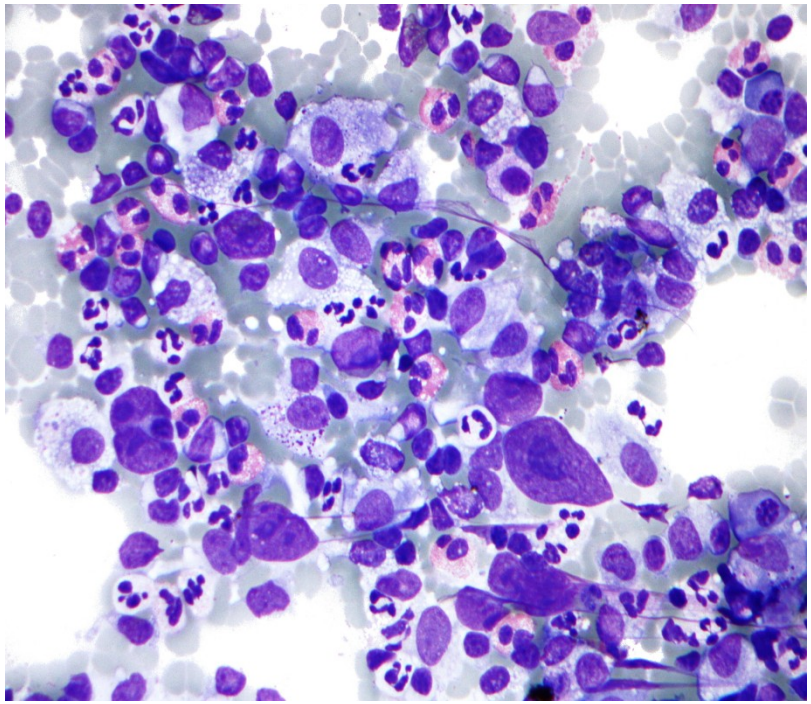
Endobronchial ultrasound-guided biopsy



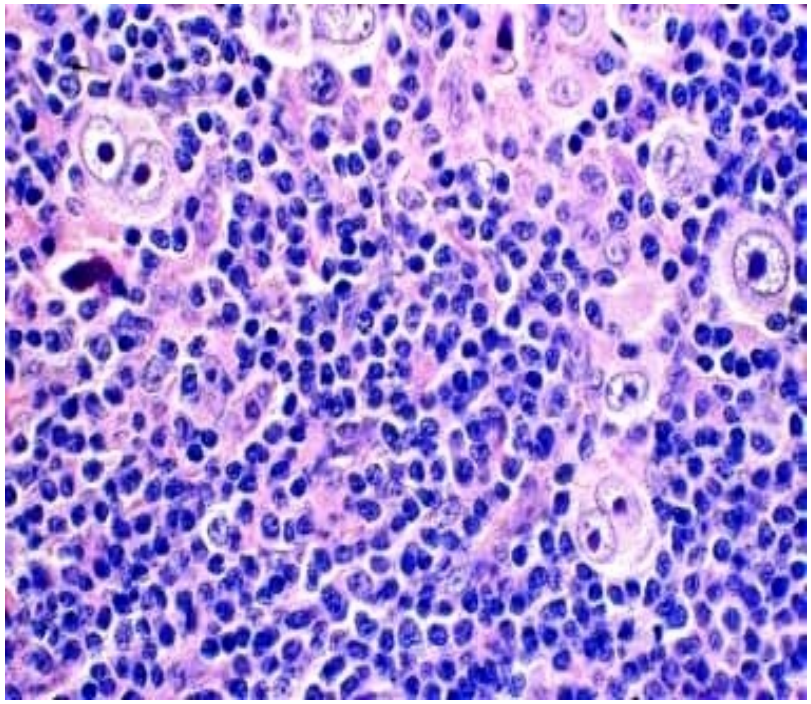
45-year-old male with 4 weeks of fever, weight loss and night sweats
Initial workup including cultures and Chest x-ray were unremarkable
Persistent elevated ESR/CRP
PET-CT shows FDG-avid lung lesions mediastinal lymph nodes
Endobronchial ultrasound-guided biopsy



Endobronchial ultrasound-guided biopsy caseating granuloma with acid-fat bacilli
Diagnosis: Tuberculous lymphadenitis
Management: Standard anti-TB therapy

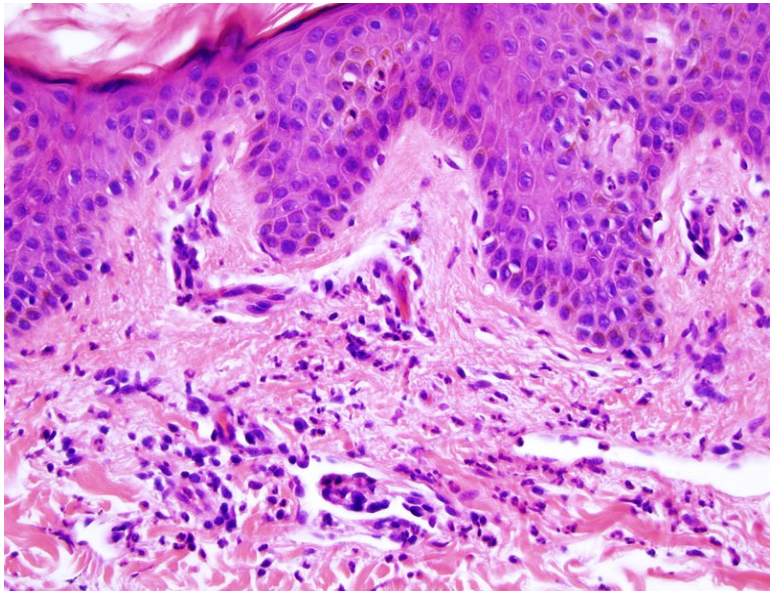


67-year-old female with 6 weeks of fever, fatigue and vague abdominal discomfort
Initial tests unrevealing
CT abdomen shows splenomegaly
And abdominal lymphadenopathy
Bone marrow biopsy performed



Bone marrow biopsy showed Hodgkin lymphoma
Diagnosis: Hodgkin lymphoma with B symptoms

32-year-old female with intermittent **fever, rash and joint pain** for 2 months
Multiple antibiotics trials without improvement
Marked elevation of ferritin (>3000)
Negative ANA, RF, blood cultures
Pink rash during fevers

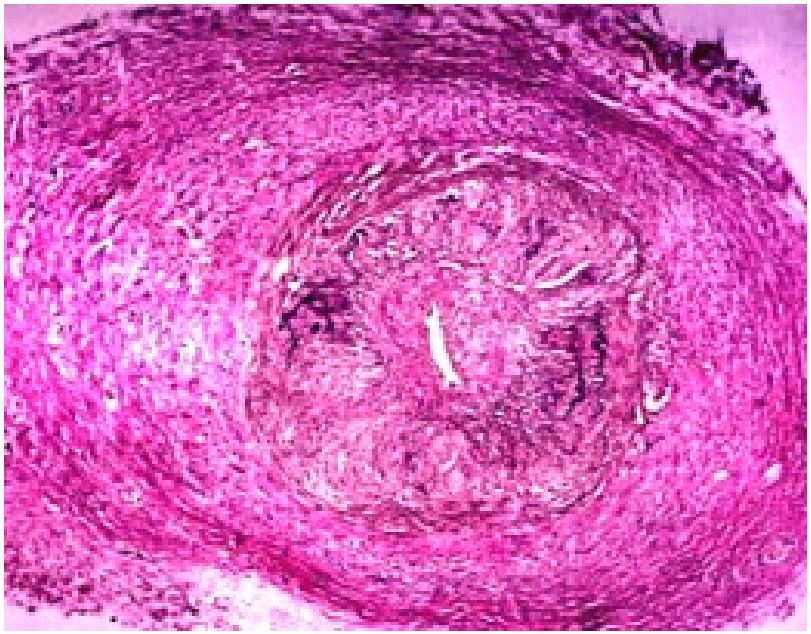


Characteristic salmon-pink rash during fevers
Diagnosis: Adult-onset Still's disease

Adult-onset Still's disease (AOSD) is an uncommon systemic inflammatory disorder characterized by **inflammatory polyarthritis, daily fever, transient salmon-pink maculopapular rash and elevated serum ferritin often in excess of 000 ng/ml**

Hypersensitivity and autoimmune disorders

- Vasculitis (giant cell arteritis, granulomatosis with polyangiitis and polyarteritis nodosa)
- Polymyalgia rheumatica
- Systemic lupus erythematosus
- Mixed connective tissue disease
- Serum sickness
- Rheumatic fever



Giant cell (temporal) arteritis

Drug fever

A wide variety of drugs can cause fever

History of allergy, skin rashes, or peripheral eosinophilia is often absent in cases of drug fever

Drug fever is likely to be constant

Discontinuation generally leads to defervescence

Agents commonly associated with drug-induced fever	
Allopurinol Captopril Cimetidine Clofibrate Erythromycin Heparin Hydralazine Hydrochlorothiazide	Isoniazid Meperidine Methyldopa Nifedipine Nitrofurantoin Penicillin Phenytoin Procainamide Quinidine

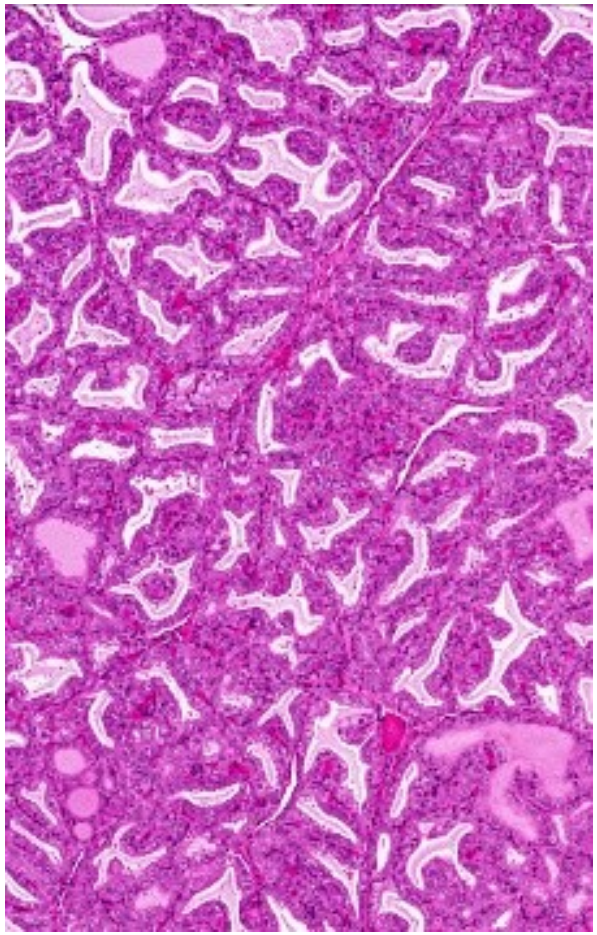
Endocrine fever

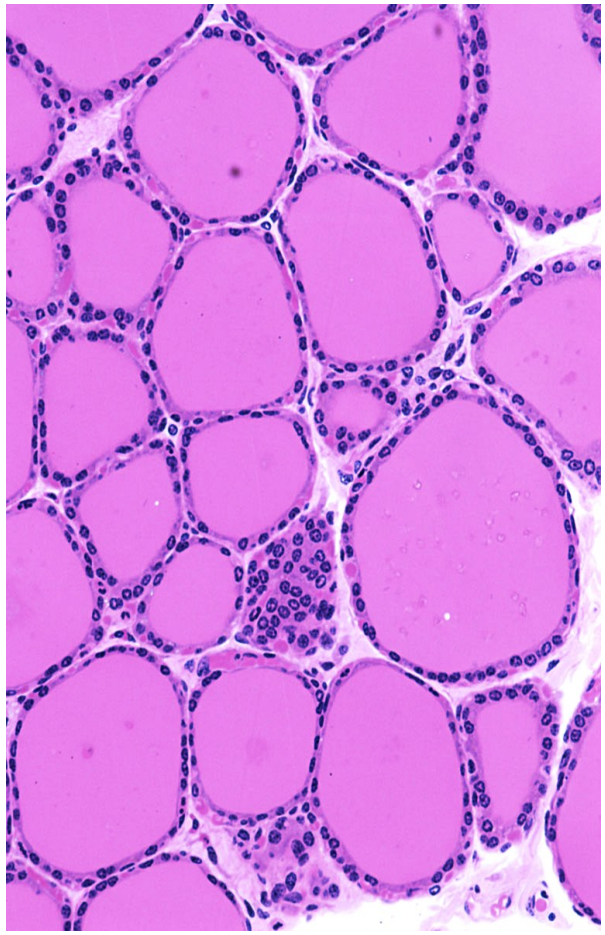
Thyroid lesions (hyperthyroidism and subacute thyroiditis)

Adrenal insufficiency

Endocrine fever to be considered in patients with nausea, vomiting, weight loss, skin pigmentation, hypotension, hyponatremia and hyperkalemia

Thyrotoxicosis





Hyperplastic thyroid

Normal thyroid

Classical FUO

- Granulomatous inflammation
- Malignant lymphoma
- Thromboembolic disease
- Endocarditis
- Vasculitis
- Intra-abdominal sepsis
- Drug fever
- Factitious

Spinal tuberculosis
Pott's disease

FUO in travelers

Parasites
Malaria, schistosomiasis, trichinella, cysticercosis

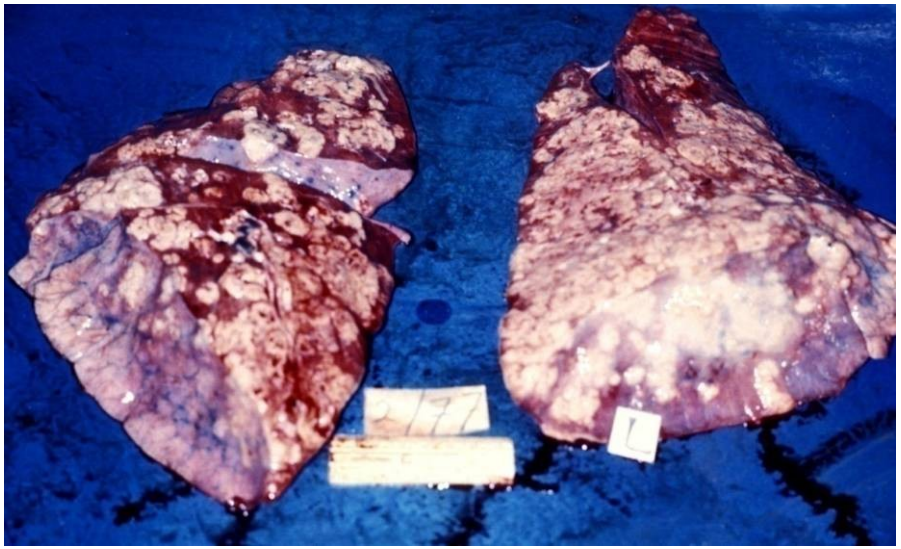
Viruses
Dengue, West Nile, Rift Valley

Fungi
Histoplasmosis, coccidiomycosis

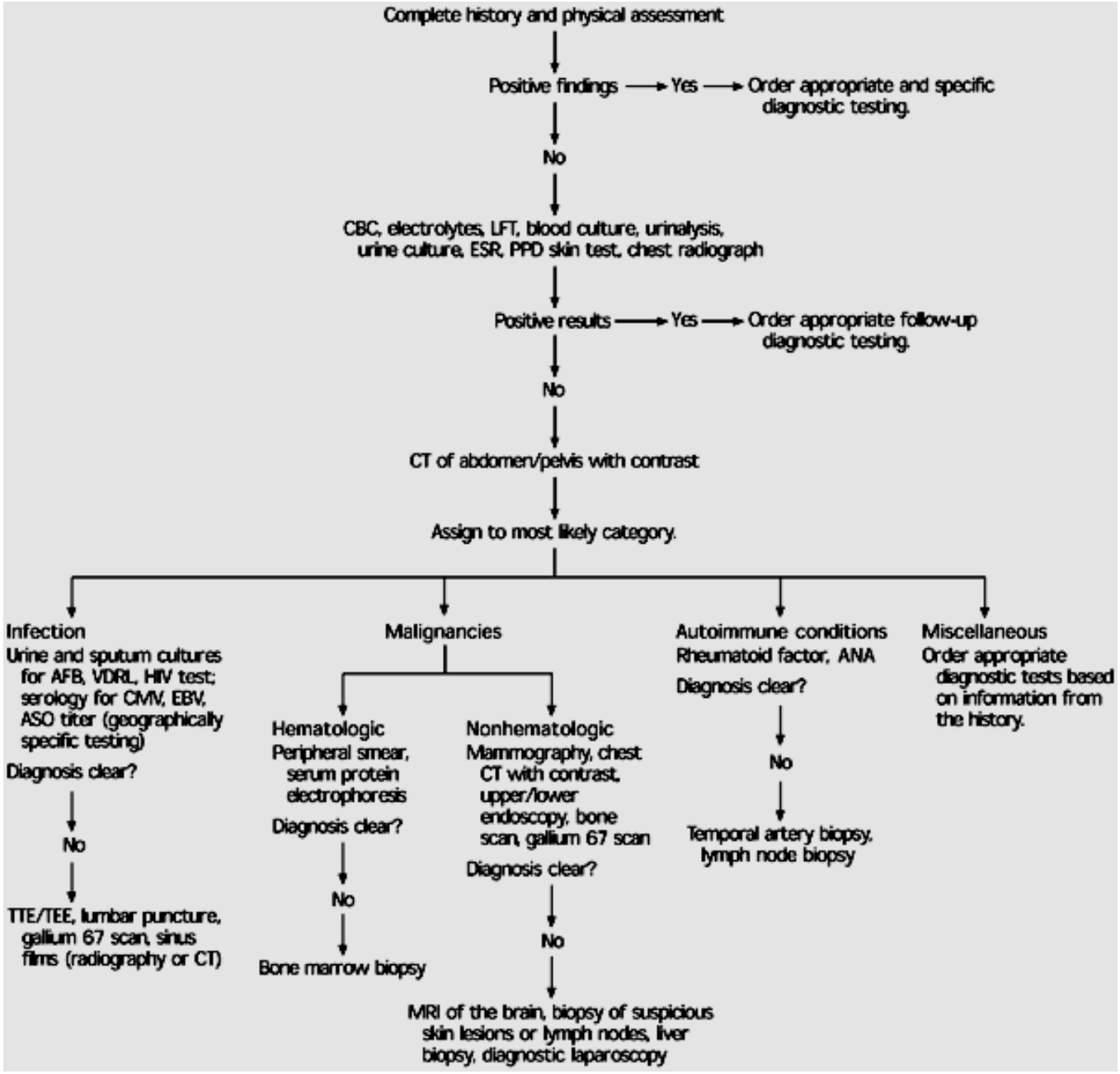
Bacteria
Melioidosis

FUO in HIV

- Pneumocystis
- Mycobacteria
- Cytomegalovirus
- Cryptococcus
- Histoplasmosis
- Bartonella
- Drugs
- Lymphoma
- Thrombophlebitis



Pneumocystis pneumonia in a patient with AIDS


Complete history and physical assessment
Positive findings
Yes
Order appropriate and specific diagnostic testing.
No
CBC, electrolytes, LFT, blood culture, urinalysis, urine culture, ESR, PPD skin test, chest radiograph
Positive results
Yes
Order appropriate follow-up diagnostic testing.
No
CT of abdomen/pelvis with contrast
Assign to most likely category.
Infection
Urine and sputum cultures for AFB, VDRL, HIV test; serology for CMV, EBV, ASO titer (geographically specific testing)
Diagnosis clear?
No
TTE/TEE, lumbar puncture, gallium 67 scan, sinus films (radiography or CT)
Malignancies
Hematologic
Peripheral smear, serum protein electrophoresis
Diagnosis clear?
No
Bone marrow biopsy
Nonhematologic
Mammography, chest CT with contrast, upper/lower endoscopy, bone scan, gallium 67 scan
Diagnosis clear?
No
MRI of the brain, biopsy of suspicious skin lesions or lymph nodes, liver biopsy, diagnostic laparoscopy
Autoimmune conditions
Rheumatoid factor, ANA
Diagnosis clear?
No
Temporal artery biopsy, lymph node biopsy
Miscellaneous
Order appropriate diagnostic tests based on information from the history.

Algorithm for the diagnosis of fever of unknown origin. CBC = complete blood count; LFT = liver function test; ESR = erythrocyte sedimentation rate; PPD = purified protein derivative; CT = computed tomography; AFB = acid-fast bacilli; HIV = human immunodeficiency virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ASO = antistreptolysin-O antibodies; ANA = antinuclear antibody; TTE = transthoracic echocardiography; TEE = transesophageal echocardiography; MRI = magnetic resonance imaging

Key Points to Remember

FUO represents a **diagnostic challenge requiring systematic approach**

Most common causes: **infections, neoplasms, autoimmune disorders, drugs**

Diagnostic strategy should progress from **non-invasive to invasive**

Advanced imaging (PET-CT) has revolutionized FUO workup

Management focuses on identifying and treating the underlying cause

~10% of cases may remain **undiagnosed** despite exhaustive evaluation